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# The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for Bipolar disorder in adults (CINP-BD-2017), part 2: Review, grading of the evidence and a precise algorithm

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## Abstract

### Background

The current paper includes the systematic search of the literature, the detailed presentation of the results and the grading of treatment options in terms of efficacy and tolerability/safety.

### Material and Methods

The PRISMA method was used in the search of the literature with the combination of the words 'bipolar', 'manic', 'mania', 'manic depression' and 'manic depressive' with 'randomized', and 'algorithms' with 'mania', 'manic', 'bipolar', 'manic-depressive' or 'manic depression'. Relevant web pages and review articles were also reviewed.

### Results

The current report is based on the analysis of 57 guideline papers and 531 published papers related to RCTs, reviews, post-hoc or meta-analysis papers to March 25th, 2016. The specific treatment options for acute mania, mixed episodes, acute bipolar depression, maintenance phase, psychotic and mixed features, anxiety and rapid cycling were evaluated with regards to efficacy. Existing treatment guidelines were also reviewed. Finally, tables reflecting efficacy and recommendation levels were created which led to the development of a precise algorithm that still has to prove its feasibility in everyday clinical practice.

### Conclusions

A systematic literature search was conducted on the pharmacological treatment of BD to identify all relevant RCTs pertaining to all aspects of BD and graded the data according to a pre-determined method to develop a precise treatment algorithm for management of various phases of BD. It is important to note that the some of the

recommendations in the treatment algorithm were based on the secondary outcome data from post-hoc analyses.

**Key Words:** Bipolar disorder, anticonvulsants, antidepressants, antipsychotics, evidence-based guidelines, lithium, mania, bipolar depression, mood stabilizers, treatment, clinical trials

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## 1. Introduction

The current paper is the second in the series of CINP papers concerning the development of a precise algorithm and clinical guidelines for the treatment of Bipolar disorder (BD) in adults for use in primary and secondary care. It includes a systematic search of the literature and a detailed presentation of the results concerning placebo-controlled randomized trials for all phases and aspects of BD. It also includes the grading of treatment options in terms of efficacy and tolerability/safety as well as a precise algorithm that still has to prove its feasibility in everyday clinical practice.

## 2. Material and Methods

As described in the first paper concerning the CINP treatment guidelines for BD, the workgroup decided that the PRISMA method (Hopewell et al., 2008; Liberati et al., 2009; Moher et al., 2009) should be followed in the search of the literature. The method included the search for three kinds of papers:

a. Randomized Controlled trials (RCTs; placebo controlled as well as clinical trials with an active comparator with the compounds used as monotherapy or add-on therapy).
b. Post-hoc analyses of RCTs
c. Meta-analyses and review papers
d. Treatment guidelines papers

For this purpose the MEDLINE was searched to March 25th 2016 with the following search strategies:

1. In order to locate RCTs, the combination of the words ‘bipolar’, ‘manic’, ‘mania’, ‘manic depression’ and ‘manic depressive’ and ‘randomized’ was used.
2. Web pages containing lists of clinical trials were scanned. These sites included http://clinicaltrials.gov and http://www.clinicalstudyresults.org as well as the official sites of all the pharmaceutical companies with products used for the treatment of BP.
3. Relevant review articles were scanned and their reference lists were utilized (Srisurapanont et al., 1995; Yatham et al., 1997; Davis et al., 1999; Burgess et al., 2001; Macritchie et al., 2001; Bech, 2002; Macritchie et al., 2003; Rendell et al., 2003; Gijsman et al., 2004; Fountoulakis et al., 2005; Gao et al., 2005; Bech, 2006; Cipriani et al., 2006a; Cipriani et al., 2006b; Rendell et al., 2006; Smith et al., 2007; Fountoulakis, 2008; Fountoulakis et al., 2008a; Fountoulakis and Vieta, 2008; Fountoulakis et al., 2009b; Yildiz et al., 2010; Cipriani et al., 2011; Nivoli et al., 2011; Tarr et al., 2011; Fountoulakis, 2012; Fountoulakis et al., 2012d; Fountoulakis et al., 2012a; Nivoli et al., 2012; Fountoulakis, 2015b, c, a).
4. The MEDLINE was searched with the combination of keywords ‘guidelines’ or ‘algorithm’ with ‘mania’, ‘manic’, ‘bipolar’, ‘manic-depressive’ or ‘manic depression’.
5. The treatment guidelines were also scanned and their reference lists were utilized

It is difficult to locate unpublished studies, especially old ones and even more difficult to retrieve their results. Thus, the main focus of this paper was on published studies which would have been peer-reviewed, are typically of higher quality and

provide more details than meeting abstracts or conference reports. However, whenever an unpublished trial was located, it is mentioned in that specific part of the manuscript. The authors decided not to seek additional information concerning unpublished trials from manufacturers as this might increase the retrieval bias.

Eventually the efficacy data were graded on the basis of a method developed by the authors and described in the first paper of the CINP guidelines for BD which is also shown in table 1. Agents were graded on the basis of safety and tolerability and these grades are also shown in table 1.

The PRISMA chart of the search process is shown in figure 1 concerning RCTs and in figure 2 concerning guidelines. Ultimately the current report was based on the analysis of 57 papers related to guidelines and 569 published papers concerning RCTs or other relevant papers (reviews, post hoc or meta-analyses).

## 3. Efficacy data

### 3a. Acute mania

The data on monotherapy and combination treatment for acute mania are shown in table 2. As well, the table also includes grading of efficacy data for various features of mania such as psychotic features, mixed features, agitation etc. most of which was based on the post-hoc analyses of RCTs.

### 3a.1 Monotherapy

#### 3a.1.1 Lithium

The first study investigating the efficacy of lithium against acute mania was conducted in 1971 but it did not follow a methodology which is accepted today as scientific standard (Stokes et al., 1971). Since then four placebo-controlled RCTs using modern clinical trial methodology starting in 1994 have been published. All of them utilized a period of 3 weeks vs. placebo, and if a comparator was included, there was an extension phase without placebo (Bowden et al., 1994; Bowden et al., 2005b; Kushner et al., 2006; Keck et al., 2009).

Overall there are 5 RCTs supporting the efficacy of lithium in comparison to placebo in acutely manic or mixed BD patients. All five are positive and the results are consistent. The overall response rate suggests a rough number needed to treat (NNT) around 5-6. The therapeutic effect appears after 7 days of treatment, that is, later in comparison to antipsychotics. There are limited data about the effect of lithium on the core symptoms of mania but there are some suggestive of an effect on psychotic features (Bowden et al., 2005b). Its effect specifically on mixed episodes is unknown and a post-hoc analysis (Swann et al., 1997) of one of these RCTs (Bowden et al., 1994) confirmed the efficacy of lithium only in classic manic but not mixed patients albeit the number of mixed patients was too small to allow firm conclusion. It exerts a therapeutic effect on manic-psychotic symptoms, but probably there is no therapeutic effect on concomitant depressive symptoms. The drop-out rate in these trials was comparable to placebo with probably more patients on placebo withdrawing from the study because of lack of efficacy while side effects were the more common

reasons for withdrawal in patients taking lithium. The most common adverse events with lithium were nausea, vomiting, dizziness headache, insomnia, asthenia, constipation, diarrhoea, tremor and weight gain.

### 3a.1.2. Antiepileptics

#### 3a.1.2.1. Valproate

Limited data concerning the efficacy of valproate in acute mania exist from earlier studies (Emrich et al., 1980; Emrich et al., 1981; McElroy et al., 1989). The first study with modern methodology on the efficacy and safety of valproate in the treatment of acute mania, was published in 1991 (Pope et al., 1991). Since then 3 positive (Pope et al., 1991; Bowden et al., 1994; Bowden et al., 2006) and 2 failed RCTs (Tohen et al., 2008b; Hirschfeld et al., 2010) were published. Another study on a heterogeneous sample consisting of bipolar spectrum disorder patients was negative (McElroy et al., 2010a). A post hoc analysis of one of the RCTs (Bowden et al., 1994) did not find any preferential effect for divalproex in classic vs. mixed manic patients (Swann et al., 1997). Overall the data support the usefulness of valproate against acute mania, although a number of issues need clarification. Its effect on psychotic symptoms is unknown and there seems to be no effect on concomitant depressive symptoms. The NNT for response is probably around 10 and the therapeutic effect is present after 5-15 days. Although the dosages utilized in these studies were higher than those usually used in everyday clinical practice (15-30 mg/kg/day), they hardly achieved the target serum concentrations (50-100 microg/mL). The most frequent adverse events were somnolence, nausea, dizziness, asthenia, constipation, twitching and vomiting.

### 3a.1.2.2. Carbamazepine

The earlier studies demonstrating the efficacy of carbamazepine in acute mania were published in the 1980s (Ballenger and Post, 1980; Post et al., 1987). Three large clinical trials using modern methodology have been published since 2000 all of which have confirmed the efficacy of carbamazepine (Weisler et al., 2004; Weisler et al., 2005; Zhang et al., 2007).

Thus, the data concerning the efficacy and safety of carbamazepine at dosages 400-1600 mg/day and a mean plasma level of 8.9 microg/mL are robust. The reported NNT is approximately 5 for response, which starts around week 2. It is unknown whether carbamazepine has a beneficial effect on the core manic symptoms, in mixed patients or against psychotic symptoms. There seems to be a beneficial effect on concomitant depressive symptoms only in mixed patients but not in manic patients (Weisler et al., 2005). The most frequent adverse events related to carbamazepine treatment were dizziness, nausea, somnolence, and an increase in total cholesterol which was composed of increases in both high-density and low-density lipoproteins.

### 3a.1.2.3. Other antiepileptics

There is one negative (BIA-2093-203) and one fixed-dosage failed (BIA-2093-204) trial for eslicarbazepine (Robertson et al., 2010). Three unpublished RCTs (NCT00107926, NCT00107939 and NCT00099229) concerning the racemic mixture licarbazepine were also negative. There are two unpublished negative trials concerning lamotrigine in treating acute manic episodes (SCAA2008/GW609 and

SCAA2009/GW610) (Goldsmith et al., 2003). Four trials concerning topiramate were all negative (Kushner et al., 2006). One small RCT evaluated the efficacy and safety of lamotrigine and gabapentin monotherapy vs. placebo in 31 patients with refractory bipolar and unipolar mood disorders. Although lamotrigine differed significantly from placebo gabapentin did not (Frye et al., 2000). Thus the data are negative for all other antiepileptics except for valproic acid and carbamazepine, which suggests that there is no class effect concerning antiepileptics in the treatment of BD (Rosa et al., 2009; Fountoulakis et al., 2011b).

### 3a.1.3. Antipsychotics

The earlier studies on antipsychotics supported the efficacy of chlorpromazine (Klein, 1967) and suggested that antipsychotics acted more rapidly although lithium was more globally effective (Shopsin et al., 1975).

#### 3a.1.3.1. Haloperidol

The efficacy and safety of haloperidol (up to 30 mg/day) was studied in five RCTs and all were positive. (McIntyre et al., 2005; Smulevich et al., 2005; Young et al., 2009; Vieta et al., 2010a; Katagiri et al., 2012). The results suggest a NNT roughly equal to 5-8 for response. The therapeutic effect is apparent as early as day 4 (Goikolea et al., 2013a). However it is important to note that there is a signal for the induction of depression in the short term (Goikolea et al., 2013b). One study reported no effect on the core symptoms of mania. However, although haloperidol might be particularly efficacious in psychotic patients, its effect on mixed patients is unknown.

Adverse events most commonly reported with haloperidol treatment were somnolence, Extrapyramidal symptoms (EPS), weight gain and constipation.

### 3a.1.3.2. Olanzapine

There are 6 positive trials supporting the efficacy of olanzapine (5-20 mg/day) for the treatment of manic or mixed episodes and concomitant psychotic features (Tohen et al., 1999; Tohen et al., 2000; Tohen et al., 2008b; McIntyre et al., 2009a, 2010b; Katagiri et al., 2012). The NNT is approximately around 5 for response (defined as a 50% drop in YMRS). Olanzapine seems to have a beneficial effect on the core symptoms of mania, on psychotic symptoms, treats mixed patients as well as rapid cycling, possibly improves coexisting depressive symptoms, and response occurs as early as days 2-7. Olanzapine does not seem to induce a switch to depression. The commonest adverse events related with olanzapine treatment were somnolence, dizziness, dry mouth, thirst and weight gain. EPS occur but at a lower rate than with haloperidol.

### 3a.1.3.3. Quetiapine

There exist 4 positive studies supporting the efficacy of quetiapine up to 800 mg/day for the treatment of acute mania (Bowden et al., 2005b; McIntyre et al., 2005; Vieta et al., 2010b; Cutler et al., 2011). Quetiapine does not seem to induce depression, on the contrary there is a clear beneficial effect on concomitant depressive symptoms. However, there is some doubt concerning its efficacy against mixed episodes (such patients were excluded in most quetiapine trials), concomitant

psychotic features, and in rapid cycling patients. The NNT is around 4-6 for response. The commonest adverse events associated with quetiapine treatment included sedation, dry mouth, somnolence, headache, dizziness and postural hypotension.

### 3a.1.3.4. Aripiprazole

There are 5 positive (Keck et al., 2003b; Sachs et al., 2006; Keck et al., 2009; Young et al., 2009; Kanba et al., 2014) and one negative fixed dosage study (El Mallakh et al., 2010), concerning the efficacy of aripiprazole 15-30 mg/day for the treatment of acute manic and mixed episodes. One study was not completed and reported no results . Again the effect on the core symptoms of mania is unknown. There is a significant effect in mixed and rapid cycling patients and it also treats concomitant positive psychotic features and agitation. Aripiprazole does not seem to induce depression but it does not seem to have any effect on concomitant depressive symptoms either. The NNT is approximately around 5-10 for response. Nausea, dyspepsia, somnolence, anxiety, vomiting, insomnia, light-headedness, constipation, and akathisia were the most common adverse events. There were no significant effects on body weight, serum prolactin or QTc prolongation.

### 3a.1.3.5. Risperidone

The efficacy of risperidone 1-6 mg/day for the treatment of acute manic and mixed episodes is supported by 3 positive studies (Hirschfeld et al., 2004; Khanna et al., 2005; Smulevich et al., 2005). The therapeutic effect is evident from day 3 onwards. It seems also effective in the treatment of positive psychotic symptoms and

agitation and concomitant depressive symptoms. The NNT is approximately around 3-5 for response. It is unknown whether risperidone has an effect on the core symptoms of mania or whether it is beneficial for rapid cycling patients. It does not seem to induce a switch to depression. Somnolence, dyspepsia, nausea and EPS were the most common adverse events.

#### 3a.1.3.6. Ziprasidone

Three positive studies (Keck et al., 2003a; Potkin et al., 2005; Vieta et al., 2010a) support the efficacy of ziprasidone 80-160 mg/day for the treatment of acute manic and mixed episodes. It has a treatment effect on the core symptoms of mania and on concomitant positive psychotic symptoms. It does not seem to have any significant effect on depressive symptoms but it also does not seem to induce a switch to depression. Its effect in rapid cycling patients is unknown. The NNT is approximately 6 for response. The commonest adverse events with ziprasidone treatment were EPS, somnolence, dizziness, anxiety, and dyspepsia. There were no significant effects on body weight or serum lipids. There was a small and clinically not significant QTc prolongation reported

#### 3a.1.3.7. Asenapine

Three positive trials (McIntyre et al., 2009a, 2010b; Landbloom et al., 2016) support the efficacy of asenapine 10-20 mg/day for the treatment of acute manic and mixed episodes with efficacy as early as day 2. It is unknown whether it has a treatment effect on the core symptoms of mania, and while in one of the studies a

positive effect on the total Possitive and Negative Symptoms Scale (PANSS) score is reported, the specific effect on concomitant positive or negative psychotic features is unknown. Unknown is also the efficacy in rapid cycling patients. The data are equivocal concerning the effect on depressive symptoms but also it does not seem to induce depression. The NNT is between 6-12 for response. The commonest adverse events related with asenapine treatment were EPS, somnolence, dizziness, sedation, fatigue, oral hypesthesia, dry mouth, weight gain and EPS.

#### 3a.1.3.8. Paliperidone

Two studies (Vieta et al., 2010b; Berwaerts et al., 2012b) provide support for the efficacy of 12 mg/day of paliperidone ER for the treatment of acute manic and mixed episodes while the data for lower dosages is conflicting. Paliperidone is effective as early as day 2. It is not reported whether it has a treatment effect on the core symptoms of mania, positive psychotic symptoms and depression and the effect in rapid cycling patients is unknown. It is unclear whether paliperidone ER can induce switches to depression. The commonest adverse events related with paliperidone ER treatment were headache, somnolence, EPS and prolactin elevation were the most common treatment-emergent adverse event.

#### 3a.1.3.9. Cariprazine

Three studies (Calabrese et al., 2015; Durgam et al., 2015; Sachs et al., 2015; Durgam et al., 2016) confirmed the efficacy of cariprazine (3-12 mg daily) vs. placebo in the treatment of acute manic or mixed episodes. The NNT for response or remission is

approximately 4-7. Cariprazine is reported to improve the core symptoms of mania but had no effect on the (Mondgomery Asberg Depression Rating Scale (MADRS). It improves the total PANSS but the specific effect on the PANSS positive subscale is unknown. Its efficacy in mixed and rapid cycling patients is unknown.

### 3a.1.4. Other agents and treatment modalities

Overall, the data for tamoxifen are positive, however, the total patient sample is still small (Zarate et al., 2007; Yildiz et al., 2008). One NIMH-sponsored clinical trial (NCT00026585) has not reported results yet. One small 3-week study was negative for verapamil (Janicak et al., 1998). The data concerning repetitive Transcranial Magnetic Stimulation (rTMS) are conflicting. There are two RCTs, one negative (Kaptsan et al., 2003) and one positive (Praharaj et al., 2009).

### 3a.1.5 Summary of monotherapy trials for acute mania

Overall there are sufficient data in the literature to support the general efficacy of a number of agents in the treatment of acute mania, however many details remain to be explored concerning many of the agents. Lithium, valproate, carbamazepine, haloperidol, olanzapine, quetiapine, aripiprazole, risperidone, ziprasidone, asenapine, paliperidone, cariprazine and probably tamoxifen are efficacious in the treatment of acute manic episodes. It should be mentioned that haloperidol probably induces depression. It is unsatisfactory that there are no controlled data concerning the usefulness of Electrocunvulsive treatment (ECT).

A significant problem for the everyday clinical practice is that the average clinician often utilizes the so-called 'class effect' in order to easily navigate among therapeutic options. However, what needs to be stressed is that while antipsychotics seem to possess a 'class effect' specific to the treatment of acute mania (possibly an antidopaminergic effect (Brugue and Vieta, 2007), there is no such effect in anticonvulsants concerning any phase of BD (Rosa et al., 2009; Fountoulakis et al., 2011b).

### 3a.2 Comparison of agents

#### 3a.2.1 Lithium vs. others

In two studies comparing lithium with valproate, the two agents were found to be equivalent. There was a tendency of valproate to manifest fewer adverse events and dropouts but its signal for efficacy in RCTs might be driven by its effect in patients with mixed features (Freeman et al., 1992; Bowden et al., 1994). A similar finding restricting the efficacy of carbamazepine to an undefined subgroup of patients in contrast to a wider efficacy of lithium that was reported by another study as well (Lerer et al., 1987). Overall the efficacy was similar to carbamazepine but with fewer adverse events (Okuma et al., 1990; Small et al., 1991). There has been a comparison of carbamazepine with lamotrigine which should be considered to be a failed study (Ichim et al., 2000). It should be noted however that lamotrigine is not an effective antimanic agent.

The comparison of lithium to chlorpromazine suggested that although chlorpromazine acts faster and might be more efficacious in more agitated patients,

this might be due to sedation alone, while lithium has again a broader effect on the core manic symptomatology (Platman, 1970; Prien et al., 1972; Shopsin et al., 1975). In contrast, the comparison of haloperidol and lithium suggested that haloperidol had a stronger and more rapid effect especially on behaviour and motor activity but without sedation, while lithium acted more evenly and comprehensively on the entire range of manic symptomatology. (Shopsin et al., 1975; Garfinkel et al., 1980).

Lithium was found to have equal efficacy to carbamazepine (Lerer et al., 1987; Okuma et al., 1990; Small et al., 1991), olanzapine (Berk et al., 1999; Niufan et al., 2008; Shafti, 2010), quetiapine (Bowden et al., 2005b; Li et al., 2008) and aripiprazole (Keck et al., 2009). In severely psychotic patients, it seems inferior to haloperidol (Shopsin et al., 1975; Garfinkel et al., 1980). Overall, lithium has a wider antimanic effect than valproate and carbamazepine but a weaker effect on psychotic symptoms and a slower onset of action in comparison to antipsychotics. Overall, lithium demonstrated a more favorable adverse effect profile in comparison to all other agents except aripiprazole and valproate.

### 3a.2.2. Valproate vs. others

In comparison to lithium, valproate was less efficacious and with a tendency to cause fewer adverse events and dropouts but its efficacy might be restricted to that specific group of patients with mixed features (Freeman et al., 1992; Bowden et al., 1994). In one small study, it was superior to carbamazepine and had a faster onset of action (Vasudev et al., 2000). In another study, it was superior to oxcarbazepine but with more frequent adverse events (Kakkar et al., 2009). It might be less efficacious

in comparison to olanzapine and with a slower onset of action, but also with fewer adverse events (Tohen et al., 2002a; Zajecka et al., 2002; Tohen et al., 2008b).

### 3a.2.3. Carbamazepine vs. others

Carbamazepine was reported to be equally effective in comparison to lithium but with a higher rate of adverse events. Its efficacy appeared somewhat restricted to an undefined subgroup of patients in contrast to a broader spectrum of efficacy of lithium (Lerer et al., 1987; Okuma et al., 1990; Small et al., 1991). In another study carbamazepine was inferior to valproate and had a slower onset of action (Vasudev et al., 2000). In two other studies carbamazepine was found equal to chlorpromazine but with fewer adverse events (Okuma et al., 1979), and equal to haloperidol but with a slower onset of action (Brown et al., 1989).

### 3a.2.4. Other antiepileptics

There is one study on lamotrigine vs. lithium which should be considered as failed probably because it was underpowered (Ichim et al., 2000). In another one oxcarbazepine was found to be inferior to valproate but with fewer adverse events (Kakkar et al., 2009).

### 3a.2.5. Haloperidol vs. others

The comparison of haloperidol with lithium suggested that haloperidol is more efficacious in severely psychotic patients and exerts its effect earlier, especially on

behaviour and motor activity but without sedation, while lithium acted more evenly and comprehensively on the entire range of manic symptomatology (Shopsin et al., 1975; Garfinkel et al., 1980). Haloperidol was found equally effective to carbamazepine but with a faster onset of action (Brown et al., 1989). Haloperidol had a faster onset of action than olanzapine but with more dropouts, and olanzapine was superior in the non-psychotic patients. Both agents were equally effective in reducing the HDRS score in mixed patients and in patients with higher depressive scores. Switch to depression occurred significantly more rapidly with haloperidol than with olanzapine. More EPS were reported with haloperidol and more weight gain with olanzapine (Tohen et al., 2003b; Katagiri et al., 2012). Haloperidol was reported to be overall superior to quetiapine and more efficacious in psychotic patients. In contrast to quetiapine it had no effect on depressive symptoms. Haloperidol-treated patients had more dropouts and more EPS (McIntyre et al., 2005). It was reported as not superior to aripiprazole and did not improve the depressive symptoms measured with the MADRS. In comparison to aripiprazole, more haloperidol treated patients switched to depression, more dropped out and EPS were more frequent with haloperidol (Vieta et al., 2005b; Young et al., 2009). Haloperidol was found similarly efficacious to risperidone (Segal et al., 1998; Smulevich et al., 2005) and superior to ziprasidone but also with more drop outs and adverse events (Vieta et al., 2010a). The comparison of 25 mg/day vs. 5 mg/day haloperidol revealed that the higher haloperidol dosage produced greater improvement than did the low dose but with more side effects (Chou et al., 1999).

In summary, haloperidol was similar in efficacy as carbamazepine (Brown et al., 1989) and olanzapine (Tohen et al., 2003b; Katagiri et al., 2012), risperidone (Segal et al., 1998; Smulevich et al., 2005) and aripiprazole (Vieta et al., 2005b;

Young et al., 2009). It was found to be superior to quetiapine (McIntyre et al., 2005) and ziprasidone (Vieta et al., 2010a) and in severely psychotic patients to lithium (Shopsin et al., 1975; Garfinkel et al., 1980). It acted faster in comparison to lithium (Shopsin et al., 1975; Garfinkel et al., 1980), carbamazepine (Brown et al., 1989) and olanzapine (Tohen et al., 2003b; Katagiri et al., 2012). Overall it demonstrated superior efficacy in psychotic patients but less improvement (if any) on depressive symptoms. It also showed more adverse events (especially EPS), switching to depression and dropouts than the comparators.

### 3a.2.6. Olanzapine vs. others

Olanzapine was reported to be equally effective to lithium but with more adverse events, mainly weight gain (Berk et al., 1999; Niufan et al., 2008; Shafti, 2010). It might be superior and faster acting in comparison to valproate (although this could be a function of dosage) but again with more adverse events (Tohen et al., 2002a; Zajecka et al., 2002; Tohen et al., 2008b). It was found to be similar in efficacy to haloperidol but with a slower onset of action and fewer dropouts. The data suggest that during the acute phase both agents were equally effective in reducing the HDRS score in mixed patients and in patients with higher depressive scores. More EPS were registered with haloperidol and more weight gain with olanzapine (Tohen et al., 2003b; Katagiri et al., 2012). Olanzapine was found superior to asenapine in manic and mixed patients and also significantly improved the MADRS score which asenapine did not. Olanzapine-treated patients had more weight gain (McIntyre et al., 2009a, 2010b).

Olanzapine was found to have similar efficacy as risperidone in patients without psychotic features, in terms of YMRS, HAM-D and MADRS change. The two agents were also equal in the subgroup of rapid cycling patients. Fewer olanzapine-treated patients dropped out of the head-to-head comparison but there was more weight gain in the olanzapine group (Perlis et al., 2006b). Finally an unpublished study of olanzapine vs. ziprasidone (NCT00329108) was stopped prematurely due to poor recruitment (2009).

### 3a.2.7. Quetiapine vs. others

Quetiapine is reported to be comparable to lithium but with more dropouts and adverse events (Bowden et al., 2005b; Li et al., 2008). Also it is reported to be inferior to haloperidol, with fewer dropouts and less frequent EPS, and also less efficacious in psychotic patients. In contrast to haloperidol it had an effect on depressive symptoms (McIntyre et al., 2005).

Quetiapine is reported to be equal to paliperidone and both agents had a similar effect in manic and mixed patients. Body weight increase was more frequent in the quetiapine group, but more patients with paliperidone switched to depression (Vieta et al., 2010b) .

### 3a.2.8. Other antipsychotics

Chlorpromazine was found equal to pimozide with faster action probably due to its greater sedative effect. Sedation was the side effect most frequent with chlorpromazine and EPS were more frequent with pimozide (Cookson et al., 1981)

The following studies have already been reported and discussed above, however it is important to consider them again from a reverse angle. Risperidone was found equal to haloperidol (Segal et al., 1998; Smulevich et al., 2005) and olanzapine (Perlis et al., 2006b). Aripiprazole was found equal to lithium (Keck et al., 2009) and haloperidol (Vieta et al., 2005b; Young et al., 2009). Asenapine was found inferior to olanzapine (McIntyre et al., 2009a, 2010b), and paliperidone equal to quetiapine (Vieta et al., 2010b). There is one unpublished study comparing ziprasidone with olanzapine which did not report any results (2009) and another one finding it inferior to haloperidol (Vieta et al., 2010a). Finally there are two studies comparing chlorpromazine with lithium (Platman, 1970; Prien et al., 1972) and one with carbamazepine (Okuma et al., 1979), suggesting equal efficacy.

### 3a.2.9. Summary of the comparison of agents

Overall, comparison studies suggest that the greater the efficacy the more frequent the adverse events are. Although there are no sufficient data to support a big difference between agents, it seems that antipsychotics and lithium are more efficacious than valproate and carbamazepine unless a loading strategy for these anticonvulsants is applied. Also it seems clear that antipsychotics act earlier in comparison to the other compounds. The effect on depressive symptoms is unclear but it seems that haloperidol-treated patients might switch more often to depression.

Earlier studies suggested that lithium could be specifically useful against the more ‘classic’ cases of euphoric mania, while antiepileptics might have a better efficacy for patients with mixed features and those with comorbidity. This is not supported by more recent data (Fountoulakis et al., 2012b). A factor which could have

affected the results is the so-called lithium-discontinuation-related refractoriness (Post et al., 1992) because of which patients enrolled in RCTs could constitute a sample more refractory to lithium treatment than expected. However, the assumption for the existence of lithium-discontinuation-related refractoriness is not supported by studies reporting that even when samples enriched for lithium refractoriness were used, no inferiority of lithium to the other agent was documented (Bowden et al., 1994). Also a recent meta-analysis of all published cases concluded that there is not sufficient data to support such a concept (de Vries et al., 2013).

### 3a.3 Combination and add-on treatment

Several studies examine the efficacy and safety of agents given not as monotherapy but combined treatments. The study samples range from patients being refractory to an initial treatment to drug-naive patients. In the first instance, an agent is used as adjunct or add-on therapy on a pre-existing treatment to which the patient has shown unsatisfactory response. In the second instance the study tests a combination treatment against monotherapy and both agents are initiated simultaneously. Although essentially both designs provide information on how to treat patients with an unsatisfactory response to monotherapy, the conclusions and the generalizability might differ.

#### 3a.3.1 Combination treatment

Adding valproate to First Generation Antipsychotics (FGAs; haloperidol or perazine in this study) produced higher response rates in manic patients (70% vs. 46%)

compared with FGA plus placebo (Muller-Oerlinghausen et al., 2000). Similarly, combination of lithium (600 to 1,800 mg/day) and quetiapine XR (400 to 800 mg/day) was superior to quetiapine plus placebo (Bourin et al., 2014) in treating acute mania. Three studies that reported on combinations of mood stabilizing agents with haloperidol vs. haloperidol monotherapy are equivocal as the outcome depended on the haloperidol dosage (Garfinkel et al., 1980; Klein et al., 1984; Chou et al., 1999).

Other studies reported on the efficacy of an antipsychotic agent and a mood stabilizer in comparison to mood stabilizer alone. In general, antipsychotic and carbamazepine combination is not superior to carbamazepine alone, primarily due to the effect of carbamazepine inducing the metabolism of antipsychotics in the combination group, thus resulting in lower plasma levels of antipsychotics. One 6-week international trial of olanzapine (10-30 mg/day) vs. placebo add on to carbamazepine (400-1200 mg/day) was negative. In the olanzapine group, however, the triglyceride levels were significantly higher and potentially clinically significant weight gain occurred more frequently. Furthermore, carbamazepine significantly reduced olanzapine serum concentrations (Tohen et al., 2008a). Similarly, in another study, carbamazepine significantly reduced the serum levels of risperidone (Yatham et al., 2003) which contributed to the negative findings of this study on the primary efficacy measure.

Overall the data on the combination of lithium with other agents support the conclusion that the combinations of lithium with haloperidol, lorazepam, carbamazepine, tamoxifen and allopurinol are superior to lithium alone, but not the combination of lithium plus ziprasidone or dipyridamole. Most of these combinations had more adverse events in comparison to monotherapy (Garfinkel et al., 1980; Lenox et al., 1992; Small et al., 1995; Weisler et al., 2003; Bowden, 2005; Machado-Vieira et al., 2008; Amrollahi et al., 2010). Adding allopurinol to treatment as usual

was not more effective compared with treatment as usual (Weiser et al., 2014). On the contrary positive results were reported by the addition of 400 mg/day celecoxib on valproate in non-rapid cycling and non-psychotic patients (Arabzadeh et al., 2015) but negative when added on ECT (Kargar et al., 2015).

A number of trials investigated the combination of an atypical antipsychotic or other agents with addition of an agent on top of lithium or valproate, since these two constituted the backbone of the treatment of bipolar disorder for decades. Overall the data are in support of combining lithium or valproate with asenapine, olanzapine, risperidone, haloperidol and tamoxifen but negative concerning gabapentin and medroxyprogesterone (Pande et al., 2000; Sachs et al., 2002; Yatham et al., 2003; Kulkarni et al., 2006; Szegedi et al., 2012; Kulkarni et al., 2014; Xu et al., 2015b). The addition of folic acid to valproate has equivocal support (Behzadi et al., 2009) and the addition of omega-3 fatty acids has negative data (Chiu et al., 2005). Adding the herbal agent Free and Easy Wanderer Plus (FEWP) on carbamazepine was not better than carbamazepine alone but it was in comparison to placebo while carbamazepine monotherapy was not. Technically it does not support the use of FEWP in acute mania, but a number of other interpretations also exist, for example that adding FEWP compensates for the drop in carbamazepine levels (Zhang et al., 2007). However that study did not define an a-priori primary outcome and therefore its quality is low. Finally, one study suggested that the valnoctamide plus risperidone combination was more effective than risperidone alone (Bersudsky et al., 2010).

In summary, there are few but still important data suggesting that specific combinations are superior to monotherapy in non-refractory or otherwise selected samples, although it is difficult to assess the quality of many study samples. Despite the very small number of trials and the problems with the data quality, one could

generalize that the combination of an antipsychotic plus lithium or valproate is superior to lithium or valproate alone, with the caveat of greater side-effect burden. Tamoxifen and probably allopurinol are also valuable agents to use in combination with mood stabilizers.

### 3a.3.2 Add-on treatment

In patients refractory to haloperidol treatment, the addition of phenytoin has been shown to be beneficial (Mishory et al., 2000). In patients refractory to lithium, adding 600-1200 mg/day carbamazepine or oxcarbazepine improved the outcome (Juruena et al., 2009) but that study was of poor quality, questionable phase of the disorder and outcome and without any a-priory defined primary outcome. Adding lovastatin on lithium was negative (Ghanizadeh et al., 2014).

In patients refractory to lithium, valproate, or carbamazepine, it is beneficial to add haloperidol, olanzapine, quetiapine, aripiprazole, or asenapine (Szegedi et al., 2012) (Sachs et al., 2002; Tohen et al., 2002b; Sachs et al., 2004; Yatham et al., 2007; Vieta et al., 2008b) but not ziprasidone, topiramate, risperidone or paliperidone (Roy Chengappa et al., 2006; Berwaerts et al., 2011; Sachs et al., 2012b, a; Moosavi et al., 2014). One study which used a mixed population with some patients entering after a minimum of 2 weeks of mood stabilizer therapy, and others starting a mood stabilizer and risperidone in parallel, provided inconclusive data for risperidone (Yatham et al., 2003) as the results were likely confounded by the effects of carbamazepine on serum levels of risperidone. Allopurinol was not beneficial in patients refractory to lithium, valproic acid, carbamazepine, or atypical antipsychotic medications (Fan et al., 2012) although there are some data suggesting a beneficial effect on patients refractory to

valproate (Jahangard et al., 2014). Adding the melatonin agonist ramelteon was also not efficacious in patients refractory to treatment as usual (McElroy et al., 2010b).

There is only one sham-controlled trial of ECT as adjunctive treatment to chorpromazine (600 mg/day) in 30 acutely manic patients. That study supported the efficacy of ECT with a faster rate of improvement (Sikdar et al., 1994)

A recent placebo-controlled 4-week RCT in 180 acutely manic patients supported the efficacy and safety of the purinergic agents allopurinol (600 mg/day) and dipyridamole (200 mg/day) as adjunctive to lithium in acute bipolar mania (Machado-Vieira et al., 2008). Folic acid was also found to be useful as an adjunct to valproate in treating acute mania (Behzadi et al., 2009) There is one 5-week trial from Israel on 32 recently admitted manic inpatients which compared valnoctamide (600-1200 mg/day; N=15) vs. placebo (N=17) on top of risperidone (1-6 mg/day). All medications were started at day 1. In all efficacy measures the valnoctamide plus risperidone combination was more effective than risperidone plus placebo from week 3 to week 5 Valnoctamide is an anticonvulsant analogue of valproate that does not undergo biotransformation to the corresponding free acid, and in mice it has been shown to be distinctly less teratogenic than valproate (Bersudsky et al., 2010). A pilot 8-week study in 21 acutely manic outpatients on the usefulness of adjunctive ramelteon in acute mania/mixed states failed (McElroy et al., 2010b), while another two on the cholinesterase inhibitor donepezil were negative (Eden Evins et al., 2006a; Chen et al., 2013).

Overall, the data in partial responders or refractory patients support the addition of specific antipsychotics to lithium or valproate and also the use of allopurinol and the combination of lithium with carbamazepine or maybe oxcarbazepine.

### 3a.4 Post-hoc analyses and meta-analytic studies

A very important post hoc analysis of individual patient data reported that patients with impaired insight (as measured with the use of item 11 of the Young Mania Rating Scale-YMRS) responded better; therefore treatment should be initiated immediately and the therapist should not wait until the patient gains sufficient insight (Welten et al., 2016).

Overall, post hoc and meta-analytic studies confirm the efficacy of specific agents vs. placebo (Emilien et al., 1996; Yatham et al., 2004; Perlis et al., 2006a; Scherk et al., 2007; Tamayo et al., 2010), and also confirm the superiority of antipsychotics versus lithium, valproate and carbamazepine both in terms of faster onset of action but also in terms of the overall outcome in the short-term treatment of acute mania. However, they also confirm that this higher efficacy comes with the cost of more frequent adverse events, mainly EPS, weight gain and somnolence (Correll et al., 2010; Tarr et al., 2010). These conclusions should be received with caution, taken into consideration the both the limitations of meta-analytical methods and the frequent conflicting results.

Haloperidol might be the fastest acting of all (Goikolea et al., 2013a) but also the most likely one to induce depression (Goikolea et al., 2013b). Olanzapine was efficacious against mixed episodes, depressive symptoms and psychotic features as well as in rapid cycling patients (Baker et al., 2002; Baldessarini et al., 2003b; Chengappa et al., 2003; Suppes et al., 2005; Suppes et al., 2008b). Quetiapine was proven efficacious for all YMRS individual items, depressive symptoms and also against psychotic features (Vieta et al., 2005a). Risperidone vs. placebo caused higher remission rate and the drop-out rate because of lack of efficacy was lower, while the

drop-out rate because of adverse events was similar to that of placebo (Gopal et al., 2005). Asenapine was efficacious against depressive symptoms (Szegedi et al., 2011), mixed episodes (Azorin et al., 2013; McIntyre et al., 2013) and has an effect on the core symptoms of mania (Cazorla et al., 2013). Aripiprazole had no effect in patients aged >55 years but was effective against psychotic symptoms (Suppes et al., 2008b; Fountoulakis et al., 2009a; Sayyaparaju et al., 2014). Aripiprazole, lithium and haloperidol overall are not efficacious against concomitant depressive features (Ostacher et al., 2015b). Ziprasidone was efficacious against dysphoric mania (Ketter et al., 2010; Stahl et al., 2010). The data of oxcarbazepine appear to be insufficient (Vasudev et al., 2011). A post hoc analysis of a lithium study (Bowden et al., 1994) confirmed the efficacy of lithium in classic manic but not mixed patients (Swann et al., 1997) while another post-hoc study confirmed the lack of efficacy of eslicarbazepine although there seems to be some signal in the secondary outcomes (Grunze et al., 2015).

Meta-analytic studies also suggest that combination treatment is superior to monotherapy at the cost of more frequent adverse events; however, these meta-analyses do not distinguish between add-on and combination studies and populations (Scherk et al., 2007; Smith et al., 2007; Tarr et al., 2011; Ogawa et al., 2014). One meta-analysis reported that studies outside the USA had higher effect size and the baseline YMRS predicted the outcome (Tarr et al., 2011) probably because of a mathematical structural coupling effect (Fountoulakis and Kontis, 2012). Year of study publication was not associated with YMRS score change. Furthermore, the study size, number of study sites, YMRS score required for study entry, inclusion of patients with mixed mania or treatment resistance, and inclusion of inpatients vs. outpatients had no significant influence on the outcome (Tarr et al., 2011).

Two recent meta-analyses attempted to rank antimanic agents according to efficacy. The first one utilized the method of multiple-treatments meta-analysis and reported that the ranking in terms of efficacy was haloperidol, risperidone, olanzapine, lithium, quetiapine, aripiprazole, carbamazepine, asenapine, valproate, and ziprasidone. According to that meta-analysis, overall, antipsychotics were significantly more effective than mood stabilizers, however the results of that analysis do not fully support such a conclusion (Cipriani et al., 2011). This meta-analysis has been criticized both concerning the overall methodology but also concerning the incomplete list of RCTs which was utilized (Fountoulakis and Siamouli, 2012). A more balanced meta-analysis confirmed that the response to antipsychotics was greater and more rapid in comparison to lithium, valproate, or carbamazepine, but it did not confirm any difference between haloperidol and second generation antipsychotics (Yildiz et al., 2010). A more recent network meta analysis did not support the superiority of any agent vs. another except for risperidone vs. aripiprazole and valproate (Yildiz et al., 2015).

A meta-analysis which pooled data from 9 randomized, double-blind, placebo-controlled, acute studies of ziprasidone reported that the discontinuation rate due to adverse events or 7% or greater weight gain between ziprasidone and placebo was not significant for all psychiatric conditions. In acute mania the risk for akathisia with ziprasidone had a Number Needed to Harm (NNH)=12, the risk for overall EPS had a NNH=12 and the reported-somnolence had NNH = 7 (Gao et al., 2013). Finally, a recent network meta-analysis reported that aripiprazole, olanzapine, quetiapine, risperidone, and valproate had less all-cause discontinuation rates than placebo and that there is a similar efficacy profile for haloperidol, second-generation antipsychotics, and mood stabilizers (Yildiz et al., 2014) while a meta-analysis of

combination studies confirmed the higher rate of adverse events in comparison to monotherapy (Galling et al., 2015).

The analysis of the data concerning the usefulness of the cholinesterase inhibitors galantamine and donepezil as well as the glutamate receptor antagonist memantine was negative (Veronese et al., 2016).

### 3b. Acute bipolar depression

Bipolar depression is not well studied, and the common practice among clinicians is to extrapolate the clinical data and wisdom from the treatment of unipolar to bipolar depression. However, the clinical trials that examined the efficacy of various agents have raised questions about the validity of such strategy.

The agents are listed below in a 'historical' sequence with lithium and anticonvulsants first, then antidepressants and finally with antipsychotics on the basis of the year of the first study they were investigated.

The data on monotherapy and combination treatment for acute bipolar depression and its special characteristics are shown in table 3.

### 3b.1 Monotherapy

#### 3b.1.1. Lithium

The earlier studies on the efficacy of lithium against bipolar depression provided some positive data but are difficult to interpret (Goodwin et al., 1969; Greenspan et

al., 1970; Stokes et al., 1971; Goodwin et al., 1972; Noyes and Dempsey, 1974; Noyes et al., 1974; Baron et al., 1975; Mendels, 1976; Donnelly et al., 1978; Srisurapanont et al., 1995). There is only one modern and rigorously conducted RCT (EMBOLDEN I) and it was negative for lithium while it was positive for quetiapine. While in this particular study the mean lithium serum levels were 0.61 mEq/lt, with 34.9% of patients having levels below 0.6 mEq/lt, a post-hoc analysis reported that the results were negative also in patients with lithium levels >0.8 mEq/lt and also in patients who completed the study. Furthermore, lithium level did not correlate with change in depression rating scores (Young et al., 2010).

### 3b.1.2. Antiepileptics

#### 3b.1.2.1. Valproate

There are three small positive trials (Davis et al., 2005; Ghaemi et al., 2007; Muzina et al., 2010) and one failed (Sachs et al., 2001) which is not published and can be assessed only through two meta-analytic papers (Bond et al., 2010; Smith et al., 2010). Taken together, these studies suggest that there are some data (though somewhat inconsistent and not sufficient), coming from small trials supporting the efficacy of valproate (titrated up to 2500 mg/day) in bipolar depression, especially in BD-I patients and on the core symptoms of depression. There is possibly some efficacy against concomitant anxiety.

### 3b.1.2.2. Carbamazepine

The old small withdrawal study concerning carbamazepine efficacy against bipolar depression were positive (Ballenger and Post, 1980; Post et al., 1983; Post et al., 1986) but also suggested that plasma levels do not correlate with the treatment effect (Post et al., 1983). A more recent 12-week double-blind, randomized, placebo-controlled study from China had equivocal results (Zhang et al., 2007).

### 3b.1.2.3. Lamotrigine

There are five trials which investigate the efficacy and safety of lamotrigine in the treatment of acute bipolar depression (SCA100223/NCT00274677, SCA30924/NCT00056277, SCA40910, SCAA2010 and SCAB2001). One included BD-II patients alone and one a mixed population of BD-I and BD-II patients. All were negative concerning the primary outcome (Calabrese et al., 1999; Goldsmith et al., 2003; Ostacher et al., 2008) although in one study lamotrigine separated from placebo on MADRS, an important secondary outcome measure (Calabrese et al., 1999). A small double-blind, randomized study with crossover series of three 6-week monotherapy evaluations, in a mixed unipolar-bipolar population reported that lamotrigine was superior to placebo (Frye et al., 2000). Overall the data are negative concerning the efficacy of lamotrigine in acute bipolar depression although the presence of a weak signal cannot be ruled out.

### 3b.1.3. Antidepressant monotherapy

Despite the fact that antidepressants have established efficacy in unipolar depression, which defines them as a class of drugs which includes different kinds of molecules, such a 'class effect' does not appear to be present for bipolar depression (Fountoulakis et al., 2011b). Although the data are problematic, the use of antidepressants is neither encouraged nor prohibited by all treatment algorithms, which however consistently advise the concomitant use of an antimanic agent. The current view is that antidepressant monotherapy should not be used in bipolar depression (Vieta, 2014). Older placebo-controlled studies were mostly positive but difficult to judge on the basis of modern criteria and understanding of methodology.

An early study reported superiority of tranylcypromine vs. placebo in anergically depressed patients and suggested that tranylcypromine could be efficacious against bipolar depression since anergic depression most typically occurs in BD and in pseudounipolar affective illnesses (Himmelhoch et al., 1982). However the methodology of this study has been criticised.

The first trial reported that fluoxetine and imipramine were efficacious vs. placebo but the interpretation of the results of this study is complicated by the concomitant use of lithium, especially in the fluoxetine group (Cohn et al., 1989). A second small trial was negative for fluoxetine and olanzapine monotherapy and also for the olanzapine-fluoxetine combination (OFC) (Amsterdam and Shults, 2005a). Another small placebo-controlled, cross-over study lasting 9 months on 10 BD-II depressed patients suggested that escitalopram might be better than placebo as monotherapy for depression and without worsening of illness course (Parker et al., 2006). The only properly conducted study on a sample of adequate size was an international trial on

740 patients with bipolar depression (both BD-I and BD-II). This study was negative for paroxetine 20 mg/day while it was positive for quetiapine. However, paroxetine produced a significant improvement in anxiety in terms of change of HAM-A scale score from baseline but was not efficacious concerning depressive symptoms in any subgroup of patients. The most frequent adverse events were dry mouth, sedation, headache, insomnia, and nausea with paroxetine treatment (McElroy et al., 2010c).

In conclusion, given that the efficacy data are conflicting along with concerns about manic/hypomanic switch, the use of antidepressant monotherapy is strongly discouraged.

### 3b.1.4. Antipsychotics

#### 3b.1.4.1. Olanzapine

An international trial supported the superiority of olanzapine (5-20 mg/day) vs. placebo in the treatment of bipolar depression. However olanzapine monotherapy was proven inferior to OFC and furthermore, the analysis of individual MADRS items suggested that in contrast with OFC, olanzapine monotherapy had no effect on the core symptoms of depression (Tohen et al., 2003c). Also, a further small study was underpowered and negative (Amsterdam and Shults, 2005a). Another small study was positive (Wang et al., 2014). It is important to note mind that in order to demonstrate a true antidepressive effect, an effect on the 'core items' of depression should be demonstrated (Bech, 2001; Lecrubier and Bech, 2007). To answer this question, another trial was conducted and the results again suggested that olanzapine (5-20 mg/day) was superior to placebo but again no effect of olanzapine was observed

on the ‘core’ depressive symptoms according to LOCF analysis but surprisingly MMRM analysis showed a significant effect on core symptoms (Tohen et al., 2012). Overall, while olanzapine separated from placebo in two large clinical trials, of bipolar depression, the data concerning its efficacy on the core symptoms of depression are equivocal.

### 3b.1.4.2. Quetiapine

Overall, there are 6 studies concerning the efficacy of quetiapine in bipolar depression. All of them were positive. Quetiapine IR or XR is reported to be efficacious at dosages of both 300 and 600 mg/day. It is important to note that quetiapine had a similar efficacy in BD-I and BD-II patients as well as in rapid cycling, and it significantly improved all the MADRS items corresponding to the core symptoms of depression and also improved concomitant anxiety (Calabrese et al., 2005b; Thase et al., 2006; McElroy et al., 2010c; Suppes et al., 2010; Young et al., 2010; Li et al., 2016)

### 3b.1.4.3. Aripiprazole

Two identically designed, 8-week, multicentre, randomized, double-blind, placebo-controlled studies (CN138-096 and CN138-146) to evaluate the efficacy and safety of aripiprazole monotherapy in depressed BD-I outpatients without psychotic features were both negative for aripiprazole (Thase et al., 2008). It has been argued that the failure of these two trials was due to the ‘catching up’ of the placebo group after week 6 rather than because of a lack of efficacy of aripiprazole, however, at endpoint the

placebo response in terms of MADRS score change in the aripiprazole studies (-10.6 and -11.5) was similar to what was observed also in the quetiapine studies (from -10.3 to -11.9) while the aripiprazole response (-11.9 and -12.3) was clearly lower to the response observed with quetiapine (from -15.4 to -17.4). Another confounding factor in these studies was that transient use of hypnotics was permitted but not after 4 weeks into the trial.

#### 3b.1.4.4. Ziprasidone

There are two negative trials (NCT00141271 and (NCT00282464) concerning ziprasidone, which were published in a single paper (Lombardo et al., 2012). The placebo responses in these trials were over 50% which might have contributed to negative results. One trial of ziprasidone in bipolar spectrum depressed patients was negative (Patkar et al., 2015).

#### 3b.1.4.5. Lurasidone

One 6-week trial in bipolar depressed patients without psychotic features reported that lurasidone (20-60 mg/day or 80-120 mg/day) was superior to placebo. Lurasidone had an effect on the core symptoms of depression. Both lurasidone groups also experienced significant improvements compared with placebo in anxiety symptoms and in patient-reported measures of quality of life and functional impairment (Loebel et al., 2014a). As this was a 6-week study, and having in mind the negative findings at endpoint (week 8) for aripiprazole while the data was positive at week 6, one might be cautious concerning the interpretation of the lurasidone data. However, the magnitude

of improvement and the absolute values of lurasidone and placebo-induced change in the MADRS score argue in favor of lurasidone.

### 3b.1.4.6. Other agents and treatment options

There is a small number of early studies on very small samples concerning the α2-adrenergic agonist clonidine, the α2-adrenergic antagonist idaxozan and Thyrotropin-releasing hormone (TRH) (Kastin et al., 1972; Jimerson et al., 1980; Osman et al., 1989). A trial concerning the usefulness of ECT has been announced (Kessler et al., 2010) but its results have not been published until now. Three other uncontrolled trials suggested that bipolar depressives respond to ECT and conflicting results exist as to whether unipolar or bipolar depression respond better although probably to a lesser extent in comparison to unipolars (Daly et al., 2001; Medda et al., 2009; Bailine et al., 2010). A recent study showed ECT to be superior to a pharmacotherapy algorithm (Schoeyen et al., 2015). There is one negative study rTMS (Nahas et al., 2003). There is a small positive study on the usefulness of Cranial Electrotherapy Stimulation in BD-II Depression (McClure et al., 2015).

### 3b.2.2. Comparison of treatment options

Since only a limited number of options for the treatment of bipolar depression exist, comparison studies are limited and often they compare agents with unproven efficacy. Some early studies were too small and are problematic concerning their methodology (Coppen et al., 1972; Kessell and Holt, 1975; Aberg-Wistedt, 1982). Overall the comparison data are sparse and they suggest antidepressants are equal in efficacy but

with a different adverse events profile (Baumhackl et al., 1989; Cohn et al., 1989; Himmelhoch et al., 1991; Grossman et al., 1999; Amsterdam and Garcia-Espana, 2000; Silverstone, 2001; Vieta et al., 2002). Clomipramine might be more efficacious than imipramine in refractory BD depressed patients (Thase et al., 1992).

However the efficacy of antidepressants should be considered in combination with the negative monotherapy data for paroxetine. The frequent use of concomitant mood stabilizers as 'background' medication complicates the interpretation of results. OFC is superior to olanzapine alone (Tohen et al., 2003c) and to lamotrigine (Brown et al., 2006) and has an effect on the core symptoms of depression. The comparison of paroxetine with venlafaxine suggests a higher switching risk for patients treated with venlafaxine (Vieta et al., 2002). The relatively higher risk of treatment emergent affective switches with venlafaxine compared to sertraline or bupropion has also been reported (Post et al., 2006). However, a more recent study reported that venlafaxine was equal to lithium and without any increase in the switch rate (Lorenzo-Luaces et al., 2016).

### 3b.2.3. Combination and add-on treatment

#### 3b.2.3.1 Combination treatment

There is one trial on BD-I depressed patients which suggested that the OFC (6 and 25, 6 and 50, or 12 and 50 mg/day) was superior both to olanzapine monotherapy and to placebo. The OFC arm was relatively small (only 86 patients) and this was one of the limitations of the study. The analysis of individual MADRS items suggested that OFC had an effect on the core symptoms of depression. In comparison to placebo and

olanzapine, the OFC arm also had a lower number of inpatients, less frequent psychotic features, more rapid cycling (which may translate in higher rates of 'spontaneous remission') and lower number of centres. All these could translate into better response and limit interpretation (Tohen et al., 2003c). Another small study was negative but also underpowered to detect any treatment effect (Amsterdam and Shults, 2005a). A second study from the US (STEP-BD), utilized a combination treatment by adding paroxetine or bupropion or placebo to a mood stabilizer. The results suggested that the two antidepressant arms did not perform significantly better than placebo on top of a mood stabilizer after 26 weeks in terms of recovery rates or transient remission. The switch rates were similar as was the drop-out rate (Sachs et al., 2007) and neither response to treatment nor switching were dose dependent (Tada et al., 2015). The third trial was a 12-week double-blind, randomized, placebo-controlled study from China which reported that carbamazepine plus the herbal FEWP (36 g/day) was superior to carbamazepine alone and to placebo, but the quality of this study is considered to be low because there was no a-priori defined primary outcome (Zhang et al., 2007).

In a small study, 21 patients with acute BD-II depression, being on therapeutic levels of lithium or valproate, were randomly assigned to treatment with the dopamine D2/D3 antagonist pramipexole (N=10) or placebo (n=11) for 6 weeks. All subjects except for one in each group completed the study. There was a superiority of pramipexole in terms of response (60% vs. 9%; p=0.02). One subject on pramipexole and two on placebo developed hypomanic symptoms (Zarate et al., 2004). Another small study randomized 17 BD depressed patients to receive adjunctive inositol or placebo for 6 weeks on lithium or valproate. The results were numerically in favor of inositol in terms of response rates (44% vs. 0%; p=0.053) (Eden Evins et al., 2006b).

### 3b.2.3.2 Add-on treatment

Overall, the data suggest that in bipolar depressed patients who experience depression while under lithium treatment, it is appropriate to add lamotrigine (van der Loos et al., 2009; van der Loos et al., 2010, 2011), the D2 antagonist L-sulpiride (Bocchetta et al., 1993) or maybe oxcarbazepine (Juruena et al., 2009) but not imipramine (Nemeroff et al., 2001). The data on adding paroxetine and amitriptyline are equivocal (Bocchetta et al., 1993; Bauer et al., 1999a; Pilhatsch et al., 2010; van der Loos et al., 2010). Imipramine and venlafaxine might pose the patients at an increased risk of switching to the opposite pole without any visible therapeutic benefit in comparison to other antidepressants (Nemeroff et al., 2001; Vieta et al., 2002)

In BD patients experiencing depression during treatment with lithium or valproate, ketamine or lurasidone could be added. Lurasidone also improves anxiety and ketamine improves suicidality in these patients. Response to a single ketamine infusion appears within minutes but does not last more than 3-4 days (Young et al., 2000; Diazgranados et al., 2010; Zarate et al., 2012; Loebel et al., 2014b; Xu et al., 2015a). However there is one unpublished failed study with lurasidone as add-on to lithum or valproate (Suppes et al., 2013; Sanford and Dhillon, 2015).

A small placebo-controlled adjunctive study of aripiprazole to lithium and citalopram was negative. However the study was underpowered and the study sample was too small to detect any differences (Quante et al., 2010).

The data on the options to treat BD patients who experience a depressed episode during treatment with mood stabilizers suggest that it is not appropriate to add ziprasidone (Sachs et al., 2011) and the data are also negative also concerning bipolar

spectrum depressed patients (Patkar et al., 2015). The antiepileptic agent topiramate and levitiracetam should be avoided because there is a risk of worsening depression and inducing suicidality (Fountoulakis et al., 2012c; Siamouli et al., 2014; Fountoulakis et al., 2015). Imipramine and venlafaxine increased the risk of switching to the opposite pole without any visible therapeutic benefits in comparison to other antidepressants (Sachs et al., 1994; Post et al., 2001; Shelton and Stahl, 2004; Post et al., 2006; Schaffer et al., 2006; Altshuler et al., 2009; Saricicek et al., 2010; Sachs et al., 2011).

The data are negative concerning the addition of memantine to lamotrigine (Anand et al., 2012) or valproate (Lee et al., 2014b; Lee et al., 2014a), ketamine to ECT (Abdallah et al., 2012), lisdexamfetamine to treatment as usual (McElroy et al., 2015) and the melatonergic antidepressant agomelatine to lithium or valproate (Yatham et al., 2016).

Another placebo-controlled study in 85 bipolar depressive patients with adjunctive modafinil (a wake-promoting agent; mean dose 177 mg/day) demonstrated improved outcomes of bipolar depression without switching to mania or hypomania. Both the response and remission rates were significantly higher in the modafinil group (44% and 39%) compared with the placebo group (23% and 18%) (Frye et al., 2007). Although that study did not report a higher risk for manic switches, it has been reported that modafinil could cause subclinical switches (Fountoulakis et al., 2008c). One published study for the treatment of acute BD-I depression with adjunct armodafinil (the longer lasting isomer of modafinil; dosage 150 mg/day; N=128)) on lithium, valproate or olanzapine was positive (Calabrese et al., 2010; Calabrese et al., 2014). However two other studies were reported to be negative (Ostacher, 2014; Ketter et al., 2015). One small study on the efficacy of the antidiabetic agent

pioglitazone as add-on to lithium in bipolar patients without diabetes mellitus was positive (Zeinoddini et al., 2015). A trial of celecoxib (400 mg/day) did not support its efficacy as an adjunct in the treatment of depressive or mixed episodes (Nery et al., 2008). One study with add-on pregnenolone (titrated to 500 mg/day) was negative (Brown et al., 2014) while a very small placebo controlled trial without an a-priori defined primary outcome suggested that adding supraphysiologic doses of levothyroxine (L-T4) to a mood stabilizer improves the outcome (Bauer et al., 2016).

Some data support the usefulness of omega-3 fatty acids as adjunctive therapy in bipolar depression but not mania but the data are conflicting and inconclusive (Stoll et al., 1999; Chiu et al., 2005; Frangou et al., 2006; Keck et al., 2006b; Frangou et al., 2007; Murphy et al., 2012; Sarris et al., 2012; Sylvia et al., 2013)

Although there is a wide consensus on the usefulness of ECT both against acute mania and acute bipolar depression and in refractory cases, controlled hard data are scant (Loo et al., 2010). A recent study suggests that ECT may be more effective than pharmacotherapy for treatment-resistant bipolar depression (Schoeyen et al., 2015). Another potential tool could be TMS, however it has been poorly investigated in bipolar depression (Dell'Osso et al., 2009). Sleep deprivation and other noninvasive circadian-related interventions could be useful add-on treatments in order to accelerate and sustain the antidepressant response (Wu et al., 2009). One study on bright light therapy in bipolar depression was negative (Dauphinais et al., 2012).

### 3b.4 Post-hoc, review and meta- analytic studies

#### 3b.4.1 Post-hoc analyses of controlled trials

A post hoc analysis of the OFC and olanzapine data (Tohen et al., 2003c) reported patients with bipolar depression receiving olanzapine or OFC had greater improvement in health-related quality of life than those receiving placebo, and additionally OFC treatment is superior to olanzapine alone (Shi et al., 2004b). A second post hoc analysis of the same data set data reported that the beneficial effect was already present at day 7. A number of alternative methods of analysis of the data (pattern analysis, survival analysis and mixed-effects regression analysis) confirmed the superiority of both olanzapine and OFC vs. placebo (Dube et al., 2007). A sub analysis of Japanese subpopulation from the second olanzapine study (Tohen et al., 2012) further supported the efficacy of olanzapine in the treatment of bipolar depression (Katagiri et al., 2013). A pooled analysis of the two olanzapine studies (Tohen et al., 2003c; Tohen et al., 2012) which utilized Last Observation Carried Forward (LOCF) data supported the efficacy of olanzapine on the core depressive items (Tohen et al., 2013).

One post-hoc analysis included two quetiapine trials (Calabrese et al., 2005b; Thase et al., 2006) and confirmed the efficacy of quetiapine as monotherapy, in comparison to placebo, for the treatment of acute depressive episodes in BD-II disorder (Suppes et al., 2008a). Another post hoc analysis of only one of these trials (Calabrese et al., 2005b) concluded that quetiapine significantly improved quality of life from week 4 onwards as well as quality of sleep (Endicott et al., 2007). A further post hoc analysis of the same study reported that the NNT was 5 for both response and remission for

quetiapine (600 and 300 mg/day) compared with placebo (Cookson et al., 2007). Another post-hoc analysis of these two quetiapine trials reported that quetiapine was effective in BD-I depressed patients already from week 1 onwards (Weisler et al., 2008).

One post-hoc analysis of pooled data from two similarly designed trials who assessed the impact of aripiprazole monotherapy (Thase et al., 2008) reported that at endpoint aripiprazole was not efficacious in the more severely depressed patients (Thase et al., 2012). The post-hoc analysis of the two negative unpublished ziprasidone monotherapy trials confirmed that ziprasidone did not show superiority over placebo at week 6 in the treatment of bipolar depression and was not efficacious in the more or less severely depressed patients (Lombardo et al., 2012).

A post-hoc analysis of a 6-weeks trial of imipramine, phenelzine or placebo reported that BD-II depressive patients respond in a similar way to unipolar patients (Agosti and Stewart, 2007).

An interesting post-hoc analysis of the lurasidone studies developed a mathematical model for the drug and placebo responses and trajectories (Chapel et al., 2016) while a meta-analysis of combination studies confirmed the higher rate of adverse events in comparison to monotherapy (Galling et al., 2015). A third analysis suggested a beneficial effect of lurasidone on functioning which was partially mediated through the improvement of depressive symptoms and partially a direct effect (Rajagopalan et al., 2016).

The meta-analysis of ketamine studies support its efficacy but suggest but the data are conflicting as to whether the therapeutic effect extends beyond day 4 and up to day 7 (Lee et al., 2015; Romeo et al., 2015).

### 3b.4.2 Review and Meta-analytic studies

A review confirmed that lamotrigine had only negative data concerning the primary outcome in acute bipolar depression (Amann et al., 2010), however there was some kind of positive signal in some of the secondary outcomes. The pooling of raw data from the lamotrigine studies found a significant effect in terms of response (HAM-D score, RR=1.27, 95% CI 1.09-1.47, p=0.002) and remission rates (MADRS score, RR=1.21, 95% CI 1.03–1.42, p=0.021). There was a significant change in the MADRS total score from baseline (p=0.04) but not in the HAM-D (p=0.08). Baseline severity of depression seemed to play a significant role and lamotrigine was superior to placebo in patients with HAM-D score >24 (RR=1.47, p=0.001) but not in those with HAM-D score < or =24 (RR=1.07, p=0.445). This meta-analysis reported an admixture of contradictory results, with lamotrigine being efficacious according to one outcome but not according to another (e.g. according to MADRS but not to HAM-D and vice versa). Also the interaction by severity was because of a higher response rate in the placebo group in the moderately ill patients, while the response rate to lamotrigine was independent of severity (Geddes et al., 2009). The efficacy of carbamazepine was supported by two other reviews (Srisurapanont et al., 1995; Yatham et al., 1997).

A number of meta-analyses which were published later, reported that only quetiapine, OFC, lurasidone and to a lesser extend olanzapine monotherapy exert efficacy in the treatment of bipolar depression. They also reported negative results for lamotrigine and aripiprazole, lithium as well as for adjunctive inositol (Cruz et al., 2010; Kemp et al., 2010; Tamayo et al., 2010; Vieta et al., 2010c; De Fruyt et al., 2011; Gao et al., 2011; De Fruyt et al., 2012; Silva et al., 2013; Citrome et al., 2014; Mukai et al.,

2014; Suttajit et al., 2014). Also, it was reported that patients who do not respond in the first two weeks of treatment are unlikely to respond eventually and would benefit from a change in treatment (Kemp et al., 2010).

Two meta-analyses using identical studies suggested there is some weak efficacy for valproate (Bond et al., 2010; Smith et al., 2010) and one suggested the same for aripiprazole (Fountoulakis et al., 2011a). Another one suggested that treatment with ziprasidone increases the risk for akathisia and reported somnolence which seemed to be dose-dependent (Gao et al., 2013). There are three meta-analysis with conflicting conclusions concerning the efficacy of antidepressants (Gijsman et al., 2004; Sidor and Macqueen, 2010, 2012; Vazquez et al., 2013) However, it is clear that a class effect is not present concerning antidepressants in bipolar depression (Fountoulakis et al., 2011b). Another meta-analysis suggested that mood stabilizer monotherapy is efficacious but the addition of an antidepressant does not increase efficacy (Van Lieshout and MacQueen, 2010).

One meta-analysis which focused on depressed patients with BD-II reported that quetiapine had compelling evidence supporting its efficacy, while there was some support for the efficacy of lithium, antidepressants, and pramipexole. The data for lamotrigine were equivocal (Swartz and Thase, 2011), while some data suggest the efficacy of stimulants, especially modafinil (Corp et al., 2014), ketamine (Fond et al., 2014; McGirr et al., 2014), and anti-inflammatory agents compared with conventional therapy alone in the treatment of bipolar depression (Rosenblat et al., 2016).

Two reviews investigated the issue of the treatment of refractory bipolar depression and concluded that the available hard data is extremely scarce and most of the strategies remain essentially experimental, however there seem to be some which are potentially efficacious and promising (Aan Het Rot et al., 2012; Sienaert et al., 2013).

One meta-analysis compared the efficacy of ECT in unipolar vs. bipolar depression and identified 6 relevant studies. It reported a similar rate of response in both disorders (50.9% vs. 53.2%) (Dierckx et al., 2012).

Finally a meta-analysis reported that the probability of receiving placebo, baseline illness severity, and trial duration, correlate with placebo response rates and/or clinical trial outcome in RCTs of pharmacotherapy for bipolar depression (Nierenberg et al., 2015), while another one was negative concerning the usefulness of galantamine, donepezil and memantine (Veronese et al., 2016).

### 3c. Maintenance treatment

The efficacy data for monotherapy for the maintenance treatment phase are shown in table 4. The data concerning the combination treatment are shown in table 5

#### 3c.1. Monotherapy

##### 3c.1.1 Lithium

There are a number of historic small studies which investigated the usefulness of lithium in the maintenance treatment of BD (Baastrup et al., 1970; Melia, 1970; Small et al., 1971; Cundall et al., 1972; Hullin et al., 1972; Persson, 1972; Prien et al., 1973b; Prien et al., 1973a; Dunner et al., 1976; Fieve et al., 1976; Fyro and Petterson, 1977; Klein et al., 1981; Christodoulou and Lykouras, 1982; Kane et al., 1982; Margo and McMahon, 1982; Mander and Loudon, 1988; Post et al., 1992). All of them

reported positive findings; however, a number of drawbacks including the obsolete methodological approach and the utilization of mixed and small samples make the results of these trials difficult to interpret.

Overall there are four randomized placebo controlled studies concerning the efficacy of lithium in the maintenance treatment of BD. One is negative/failed (Bowden et al., 2000) and three are positive (Bowden et al., 2003; Calabrese et al., 2003b; Weisler et al., 2011). The fourth is a small discontinuation study (Kafantaris et al., 2004). Two of the positive studies support the usefulness of lithium in the prevention of manic but not depressive episodes irrespective of the polarity of the index episodes (Bowden et al., 2003; Calabrese et al., 2003b). The third study also supports its usefulness in the prevention of depressive episodes (Weisler et al., 2011). There are no data on the efficacy concerning the prevention of mixed episodes or for rapid cycling patients. It is important to note that the study samples were not enriched for response to lithium. On the contrary, one study had a sample enriched for response to quetiapine (Weisler et al., 2011), while two others had samples enriched for lamotrigine (Bowden et al., 2003; Calabrese et al., 2003b) which, however, is not efficacious against acute mania. There are some problems with the design of the studies, especially concerning the magnitude of improvement during the acute treatment phase and the duration the patients were required to be stable before entering the double-blind phase. With a few exceptions, most are essentially relapse prevention, not maintenance studies.

### 3c.1.2. Antiepileptics

#### 3c.1.2.1. Valproate

As mentioned above, there is one properly conducted trial (Bowden et al., 2000) in which valproate was the agent under investigation. Lithium served as active control, and since, as shown above, lithium has proven efficacy during the maintenance phase of BD, this specific trial is best considered to be a failed study and not negative for valproate.

#### 3c.1.2.2. Carbamazepine

Concerning carbamazepine, there is only one small placebo controlled study. Although carbamazepine was effective in 60% of cases relative to 22% in the placebo group, the differences were not significant likely due to lack of power. Further, there were methodological issues with the study design and hence, the data are difficult to interpret (Okuma et al., 1981).

#### 3c.1.2.3. Lamotrigine

Overall there are three placebo controlled RCTs concerning the efficacy of lamotrigine in the maintenance treatment of BD. Two of them suggest lamotrigine is efficacious in the prevention of depressive but not manic episodes irrespective of the polarity of the index episodes (Bowden et al., 2003; Calabrese et al., 2003b). There are no data concerning index mixed episodes. The only study in rapid cycling patients

was negative concerning the primary outcome (Calabrese et al., 2000). All studies were enriched for tolerability to lamotrigine, but one should have in mind that lamotrigine is neither efficacious against acute mania nor acute bipolar depression. There were some problems with the design of the studies, particularly concerning the magnitude of improvement during the acute treatment phase and the duration the patients were stable before entering the double-blind phase. Essentially they were relapse prevention, not maintenance studies.

### 3c.1.3 Antidepressants

There are 2 small old negative studies concerning the efficacy of imipramine (Prien et al., 1973a; Kane et al., 1982), while on the contrary, 3 other small studies in BD-II patients provide some support for the usefulness of fluoxetine monotherapy in the prevention of depressive episodes (Amsterdam et al., 1998; Amsterdam and Shults, 2005b, 2010).

### 3c.1.4 Antipsychotics

#### 3c.1.4.1 Olanzapine

Three trials provide support for the efficacy of olanzapine in the prevention of manic, depressive or mixed episodes in patients with an index manic or mixed episode which responded to olanzapine treatment during the acute phase (Tohen et al., 2006; Berwaerts et al., 2012a; Vieta et al., 2012). There is some data to support the notion that the efficacy of olanzapine is not restricted to those patients who responded to

olanzapine during the acute phase. Its long-term effects in rapid cycling patients are unknown.

### 3c.1.4.2 Aripiprazole

There are two trials which support the efficacy of aripiprazole in the prevention of manic but not depressive episodes in BD patients after an index manic or mixed episode who responded to aripiprazole during the acute phase (Keck et al., 2006a; Keck et al., 2007). These two trials utilize a methodology which satisfies stringent criteria concerning the definition of 'maintenance' treatment.

### 3c.1.4.3 Quetiapine

There is one published positive study which investigated the efficacy and safety of quetiapine IR monotherapy (300-800 mg/day) as maintenance treatment in BD-I patients compared with switching to placebo or lithium. The time to recurrence of any mood event was significantly longer for both quetiapine and lithium vs. placebo. Both quetiapine and lithium significantly increased time to recurrence of both manic and depressive episodes compared with placebo (Weisler et al., 2011). A second study in patients who had recovered from bipolar depression reported that quetiapine prevented depressive but not manic episodes (Young et al., 2014).

### 3c.1.4.4 Paliperidone

There is one positive study which supports the usefulness of paliperidone in the prevention of manic but not depressive recurrences in patients with index manic or mixed episodes who responded to paliperidone during the acute phase (Berwaerts et al., 2012a).

### 3c.1.4.5 Risperidone long-acting injectable (RLAI)

Two studies support the efficacy of RLAI in the prevention of manic but not depressive episodes in BD-I patients with a manic or mixed index episode who responded to oral risperidone or RLAI during the acute phase (Quiroz et al., 2010; Vieta et al., 2012).

### 3c.1.5 Conclusion of monotherapy trials

Lithium, olanzapine, quetiapine, aripiprazole, paliperidone and RLAI are efficacious in the prevention of manic episodes in patients who recovered from an index manic or mixed episode. Olanzapine and quetiapine are also efficacious in the prevention of depressive episodes. Quetiapine was efficacious irrespective of the index episode. Olanzapine was also efficacious in the prevention of mixed episodes. There is a lack of data concerning carbamazepine or valproate.

Lamotrigine is efficacious in the prevention of depressive but not manic episodes irrespective of index episode. It was not efficacious in the prevention of mixed episodes or in rapid cycling patients. The literature does not support the efficacy of

imipramine while, on the contrary, it gives some support for the efficacy of fluoxetine but only in BD-II patients.

All except lithium and olanzapine were proven efficacious only in samples enriched for response or tolerability during the acute phase. Except from the negative data for lamotrigine there are no data concerning rapid cycling patients. Also, except from the data concerning olanzapine, there are no data concerning specifically the prevention of mixed episodes or the response of patients with an index mixed episode.

### 3c.2. Comparison of treatments

#### 3c.2.1 Lithium vs. others

There are a number of studies comparing lithium with carbamazepine (Placidi et al., 1986; Watkins et al., 1987; Lusznat et al., 1988; Stoll et al., 1989; Small et al., 1991; Coxhead et al., 1992; Simhandl et al., 1993; Denicoff et al., 1997; Hartong et al., 2003) including the MAP study (Greil et al., 1997; Greil and Kleindienst, 1999a, b; Kleindienst and Greil, 2000, 2002), and overall the data suggested that both agents are comparable in terms of efficacy. There are some data in favour of a superiority of lithium in the treatment of more 'classic' patients, but in the rest of patients the two agents seem to be comparable. Lithium was also comparable to valproate in terms of prevention of mood episodes (Bowden et al., 2000; Calabrese et al., 2005a) and suicidality (Oquendo et al., 2011), to olanzapine (Tohen et al., 2005) and also to aripiprazole (El-Mallakh et al., 2012)

Furthermore, there was a difference in the clinical profiles of lithium and lamotrigine. As mentioned before, 3 placebo-controlled RCTs suggest that lamotrigine was more

efficacious in the prevention of depressive episodes and lithium in the prevention of manic, hypomanic, and mixed episodes (Bowden et al., 2003; Calabrese et al., 2003b).

When compared to antidepressants, the available data suggest that lithium is superior to imipramine for the prevention of depression in BD-I patients episodes (Prien et al., 1973a; Prien et al., 1984) but inferior to fluoxetine in BD-II patients (Amsterdam and Shults, 2010).

A maintenance study reported equal efficacy between venlafaxine and lithium in the prevention of depressive relapses although there was a tendency of better performance for venlafaxine (Amsterdam et al., 2015)

### 3c.2.2 Antiepileptics vs. others

The studies comparing valproate with lithium have already been discussed above (Bowden et al., 2000; Calabrese et al., 2005a; Oquendo et al., 2011). Two trials suggested valproate is comparable with olanzapine (Tohen et al., 2003a) and with a similar cost to healthcare system (Zhu et al., 2005). Carbamazepine has been studied only in comparison to lithium and these studies have been discussed previously in the paragraph concerning lithium (Placidi et al., 1986; Watkins et al., 1987; Lusznat et al., 1988; Small et al., 1991; Coxhead et al., 1992; Simhandl et al., 1993; Denicoff et al., 1997; Greil et al., 1997; Greil and Kleindienst, 1999a; Kleindienst and Greil, 2000, 2002; Hartong et al., 2003).

### 3c.2.3 Olanzapine vs. others

The comparison of olanzapine with lithium (Tohen et al., 2005) and valproate (Tohen et al., 2003a; Zhu et al., 2005) have been discussed above.

One study which constituted the extension of an acute phase trial suggested that olanzapine is comparable with asenapine (McIntyre et al., 2010a) while another suggested that it is superior to paliperidone ER (Berwaerts et al., 2012a) and to long-acting risperidone (Vieta et al., 2012).

### 3c.2.4 Other comparisons

The comparisons of aripiprazole (El-Mallakh et al., 2012), fluoxetine (Amsterdam and Shults, 2010) imipramine (Prien et al., 1984) and lamotrigine (Bowden et al., 2003; Calabrese et al., 2003b) with lithium, and of asenapine (McIntyre et al., 2010a), paliperidone and risperidone with olanzapine (Berwaerts et al., 2012a; Vieta et al., 2012) have been discussed previously.

One 25 week RCT comparing the OFC vs. lamotrigine in the prevention of bipolar depression reported that bipolar depressive patients who responded to OFC do better on long-term OFC in comparison to spontaneously improved patients on long-term lamotrigine (Brown et al., 2009). The result is difficult to interpret as there was an enrichment of the OFC arm, but not the lamotrigine arm. Finally, one study compared the efficacy of venlafaxine in the prevention of bipolar vs. unipolar depression and reported no difference between groups (Amsterdam and Garcia-Espana, 2000).

### 3c.3. Combination and add-on treatment

#### 3c.3.1. Combination treatment

There are three early studies which investigated the combination of lithium with another agent. The lithium plus imipramine combination was not more efficacious than lithium monotherapy (Kane et al., 1982; Prien et al., 1984) and lithium or carbamazepine monotherapy was not inferior to their combination which, however, was more efficacious in rapid cycling patients (Denicoff et al., 1997). Also the combination of lithium, carbamazepine, or valproate with perphenazine was not better than mood stabilizer monotherapy; on the contrary, combination treatment was associated with a shorter time to depressive relapse, more drop-outs, and increased rates of dysphoria and depressive symptoms (Zarate and Tohen, 2004). Similarly negative were the results for the lithium or valproate combination with olanzapine (Tohen et al., 2004) while, on the contrary, the combination with quetiapine had significant advantages irrespective of index episode, mood stabilizer and rapid cycling status (Vieta et al., 2008a; Suppes et al., 2009). Positive results were also reported for their combination with ziprasidone (Bowden et al., 2010). Results were negative for aripiprazole plus valproate (Woo et al., 2011) or lamotrigine (Carlson et al., 2012).

The OFC was similar to lamotrigine in terms of incidence of relapse but overall bipolar depressive patients who responded to OFC do better on long-term OFC in comparison to spontaneously improved patients on long-term lamotrigine (Brown et al., 2009). Lamotrigine plus divalproex was not superior to lamotrigine alone concerning the time to depressive episode (Bowden et al., 2012).

The open-label BALANCE study results neither reliably confirmed nor refuted a benefit of valproate-lithium combination therapy compared with lithium monotherapy, but clearly demonstrated that it is superior to valproate alone (Geddes et al., 2010). Another study reported that risperidone or olanzapine adjunctive therapy for 24 weeks is beneficial but continuation of risperidone beyond this period does not reduce the risk of relapse. Whether continuation of olanzapine beyond this period reduces relapse risk remains unclear but the potential benefit needs to be weighed against an increased risk of weight gain (Yatham et al., 2015).

Overall, there is no compelling data that combination treatment in general does better than monotherapy. Patients stabilized on combination treatment might, however, do worse if shifted to monotherapy, and combination treatment with quetiapine or ziprasidone plus a mood stabilizer might work better than a mood stabilizer alone.

### 3c.3.2. Add-on treatment

A small study supported the adding of phenytoin to treatment as usual (Mishory et al., 2003) as did another small one for gabapentin (but not on top of antipsychotics) (Vieta et al., 2006). The data are negative for the addition of oxcarbazepine (Vieta et al., 2008c) and equivocal for lamotrigine (van der Loos et al., 2011) to lithium. Negative data were also reported from a trial of adjunctive pramipexole to treatment as usual (TAU) in stabilized BD patients with the aim to improve neurocognition (Burdick et al., 2011), and from a trial of N-acetyl cysteine on TAU in patients after an index episode of bipolar depression (Berk et al., 2012). It is interesting that adjunctive RLAI on TAU significantly prolongs the time to relapse in rapid cycling

patients (Macfadden et al., 2009). Adding aripiprazole to lithium or valproate also supplied positive results (Marcus et al., 2011).

It is reported that patients who respond to treatment with lithium, valproate or carbamazepine plus antidepressants are more likely to maintain response with continuation of the combined treatment; however, those patients who manifest only a partial acute response are unlikely to further improve when the same treatment is continued (Altshuler et al., 2009). Also adjunctive asenapine to lithium or valproate was well tolerated for up to 52 weeks, but no efficacy data were reported from that trial (Szegedi et al., 2012).

Two trials investigated the efficacy of adjunctive N-acetyl cysteine (NAC). The first one randomized 75 BD patients during the maintenance phase and reported that NAC treatment caused a significant improvement on the MADRS score in comparison to placebo ($p=0.002$). Improvements were lost after washout. There was no effect of NAC on time to a mood episode and no significant between-group differences in adverse events (Berk et al., 2008) The second randomized 14 patients (not all of them with high depression scores) and reported a superiority of the NAC group vs. placebo in terms of remission ($p=0.031$) (Magalhaes et al., 2011b). One maintenance study supported the usefulness of ramelteon in the prevention of relapse in BD patients (Norris et al., 2013) Negative results have been reported for the usefulness of memantine in patients on valproate treatment (Lee et al., 2014b).

There are some studies suggesting that there is a role for various nutritional supplements such as n-3 fatty acids, chromium, choline, magnesium and tryptophan alone or in combination with pharmacotherapies for the treatment of BD but the data are of low quality (Sylvia et al., 2013)

### 3c.4. Post-hoc, reviews and meta-analytic studies

#### 3c.4.1 Post-hoc analyses

A number of post-hoc analyses exist and attempt to answer questions that the original papers did not address. Post-hoc analysis can be informative but can also be a major source of publication bias (Vieta, 2007). A subanalysis of the MAP study reported that lithium was superior in 'classical' BD-I patients and comparable with carbamazepine in the rest. An additional sub-analyses including mixed states as an additional non-classical feature confirmed the results (Greil et al., 1998).

Concerning the usefulness of antidepressants, one post-hoc analysis suggested that the discontinuation rate for any reason was lower among patients in the divalproex group taking a selective serotonin re-uptake inhibitor (SSRI) than among patients in the placebo group taking an SSRI (Gyulai et al., 2003b) while the application of four different remission criteria suggested that the application of different definitions of remission does not make any significant difference concerning the results (Pae et al., 2012). The addition of an atypical antipsychotic-antimanic agent in some BD patients might help to reduce suicidal ideation (Houston et al., 2006). Olanzapine might be more beneficial if started at an earlier stage of the disease (Ketter et al., 2006), and it is also efficacious in patients with an index mixed episode (Tohen et al., 2009).

Concerning lithium, it has been reported that only at plasma levels between 0.6-1.2 mEq/lt it is efficacious in the prevention of both manic and depressive episodes (Nolen and Weisler, 2013). Another post-hoc analysis did not confirm its efficacy in the prevention of depressive episodes while it confirmed the efficacy of lamotrigine in the prevention of both manic and depressive episodes irrespective of index episode

(Calabrese et al., 2003a; Goodwin et al., 2004). These results still held true when early relapses that occurred in the first 90 or 180 days were excluded from the analysis (Calabrese et al., 2006). The lack of efficacy of lithium in a subgroup of patients might be due to lithium induced thyroid function abnormalities in a subpopulation of patients (Frye et al., 2009). Overall, lamotrigine performed better in comparison with lithium in terms of remission and the persistence of subsyndromal symptoms (Frye et al., 2006). Some positive results for NAC were also suggested by two post-hoc analysis (Magalhaes et al., 2011a, 2013)

### 3c.4.2 Review and meta-analyses

One review confirmed the efficacy of lithium but reported that there is no definitive evidence as to whether or not lithium has an anti-suicidal effect (Burgess et al., 2001). A more recent meta-analysis confirmed the antisuicidal effect of lithium vs. placebo but not its superiority over other agents except carbamazepine (Cipriani et al., 2013). Two other studies support the usefulness of RLAI (Bobo and Shelton, 2010) and of ziprasidone for the maintenance treatment of BD-I disorder in adults as an adjunct to lithium or valproate (Citrome, 2010). Another review identified four issues that limit the interpretation of trials (insufficient duration, enriched sample, possible conflation with iatrogenic adverse effects by abrupt medication discontinuation with beneficial effects on treatment, and a low overall completion rate) (Tsai et al., 2011).

Concerning meta-analysis, the first one for carbamazepine failed to prove the prophylactic efficacy (Dardennes et al., 1995). A second one concluded that the data for oxcarbazepine are of very low quality not allowing firm conclusions (Vasudev et al., 2008). A fair number of meta-analyses focused on lithium. One confirmed its

efficacy but failed to find sufficient evidence to prove that a lithium-withdrawal relapse phenomenon exists, that is patients relapse soon after stopping lithium and the symptomatology turns refractory to treatment (Davis et al., 1999). Another one supported an anti-suicidal efficacy of lithium (Tondo et al., 2001). Three others confirmed the prophylactic anti-manic efficacy of lithium but were equivocal for the prophylactic efficacy against depressive episodes (Burgess et al., 2001; Geddes et al., 2004; Severus et al., 2014).

Furthermore, a number of meta-analytic studies confirmed the prophylactic antimanic efficacy of specific agents and the anti-depressant of others. It is important to mention that among other more or less expected results, the antidepressant efficacy of valproate and imipramine was supported (Beynon et al., 2009) as well as of lithium (Popovic et al., 2010), while the prophylactic antidepressant efficacy of olanzapine was questioned (Cipriani et al., 2010). Antipsychotics might be superior to lithium and anticonvulsants but with more adverse effects (Vazquez et al., 2015b; Vazquez et al., 2015a).

The issue of combination treatment has been the focus of two meta analyses. They both reported negative conclusions for the addition of antidepressants (Ghaemi et al., 2008; Beynon et al., 2009). A third analysis suggested that no monotherapy was associated with a significantly reduced risk for both manic/mixed and depressive relapse, and only quetiapine plus lithium or divalproex was associated with a significantly reduced risk for relapse towards both the manic/mixed and depressive pole (Vieta et al., 2011). This specific meta-analysis also pointed out that the majority of studies included samples enriched for response to a specific agent during the acute phase.

Finally, pharmaco-epidemiological data suggest that valproate and lithium might have a protective effect against any psychiatric hospitalization for patients with BD in a real world setting while lamotrigine and carbamazepine might exert protective effects solely against depressive and manic episodes, respectively (Joas et al., 2015).

### 3.d. Treatment of mixed episodes

Mixed episodes are no longer accepted as a diagnostic entity by DSM-5; instead 'mixed features' is included as a specifier and this creates a degree of confusion for future treatment recommendations since the two concepts differ significantly (Fountoulakis, 2015d). So far, mixed episodes have been combined with pure manic episodes in RCTs and results have been reported together. Only few papers – usually post-hoc analyses- report the results concerning mixed episodes separately. Unfortunately all data on mixed episodes stem from trials of acute mania and only one trial reports on the efficacy of lurasidone in bipolar depressive patients with mixed features. That trial supported the efficacy of lurasidone in these patients for the improvement of both depressive and manic symptoms (McIntyre et al., 2015; Suppes et al., 2015). Another important limitation is that the results reported usually concern only the manic but not the depressive component of the mixed episode (Fountoulakis et al., 2012b). The ranking of the data for the treatment of mixed episodes is shown in table 6.

### 3.d.1 Treatment of acute mixed episodes

Aripiprazole and carbamazepine were found efficacious in the treatment of both the manic and the depressive component of acute mixed episodes (Keck et al., 2003b; Weisler et al., 2004; Weisler et al., 2005; Sachs et al., 2006; Weisler et al., 2006; Suppes et al., 2008b). Ziprasidone was also found to be efficacious against both components, but the definition of mixed states was different from the DSM. Olanzapine and valproate were reported to be efficacious against mania but the data are inconclusive concerning the depressive component (Tohen et al., 1999; Tohen et al., 2000; Baker et al., 2003; Baldessarini et al., 2003b; Shi et al., 2004a; Bowden et al., 2006; Ghaemi et al., 2007; McIntyre et al., 2009b). The post-hoc analysis of the two bipolar depressive trials suggested that olanzapine was efficacious in those patients with mixed features suggesting an effect also on the depressive component (Tohen et al., 2014). Furthermore, risperidone but not asenapine is reported to be efficacious against the manic component but no data exist concerning their efficacy on the depressive component (Khanna et al., 2005; McIntyre et al., 2009b). A post hoc analysis suggested that asenapine but not olanzapine improved the quality of life in mixed patients (Michalak et al., 2014) and another two suggested that asenapine improved both the manic and depressive component in comparison to placebo and was also found superior to olanzapine concerning the manic but not the depressive component (McIntyre et al., 2013; Berk et al., 2015). However a more recent trial was negative (Landbloom et al., 2016). Paliperidone was efficacious only against the manic component (Vieta et al., 2010c; Berwaerts et al., 2012b). One study for quetiapine was a failed one (Cutler et al., 2011).

The combination of olanzapine olanzapine plus lithium or valproate have positive data concerning both components (Tohen et al., 2002b; Baker et al., 2004; Houston et al., 2006; Houston et al., 2009; Houston et al., 2011). In mixed depression the OFC was comparable to olanzapine and both were superior to placebo but due to the small number of subjects the report does not permit to derive conclusions (Tohen et al., 2003c; Benazzi et al., 2009). The data concerning the combination of haloperidol or risperidone plus lithium or valproate were negative (Sachs et al., 2002). Overall it seems that second generation antipsychotics (SGAs) are effective in treating acute mixed episodes of BD, with predominant manic symptoms. Their efficacy in treating depressed mixed episodes remains unclear (Muralidharan et al., 2013).

The only trial in patients in bipolar depressive episode with mixed features supported the efficacy of lurasidone in these patients for the improvement of both depressive and manic symptoms (McIntyre et al., 2015; Suppes et al., 2015).

### 3.d.2 Maintenance treatment of mixed bipolar episodes

The data so far suggest that olanzapine prolongs time to relapse into any episode in patients with an index mixed episode (Tohen et al., 2006; Tohen et al., 2009) while on the contrary, lithium and valproate had negative results in patients with a dysphoric manic index episode (Bowden et al., 2005a). Additionally, the data are in support of the combination of quetiapine plus lithium or valproate (Vieta et al., 2008a; Suppes et al., 2009) but are negative concerning aripiprazole in patients with an index mixed episode (Yatham et al., 2013a).

### 3.e. Treatment of rapid cycling patients

The treatment of rapid cycling patients constitutes a challenge. Often their course frustrates the therapist and the evaluation of treatment is difficult because of the rapid switching from one pole to another (Fountoulakis et al., 2013). The ranking of the treatment of rapid cycling patients is shown in table 7

#### 3.e.1. Treatment of acute episodes in rapid cycling patients

Olanzapine is effective in reducing symptoms of mania and was well tolerated in rapid cycling BD-I patients as shown by a secondary analysis (Sanger et al., 2003). The pooling of data from two RCTs reported that improvement of mania with olanzapine was similar in rapid cyclers and non-rapid cyclers. However, rapid cyclers showed an earlier response (Vieta et al., 2004). One trial was also positive concerning aripiprazole in acutely manic rapid cycling patients (Sachs et al., 2006).

Although one study on acute mania in rapid cycling patients was a failed one (Cutler et al., 2011), one *a priori* planned sub-analysis of data from rapid cycling patients with acute BD-I or BD-II depression suggested that quetiapine monotherapy (300-600 mg/day) was effective and well tolerated (Vieta et al., 2007). The post-hoc analysis of the rapid cycling subsample of bipolar depressives from the BOLDER study confirmed this (Cookson et al., 2007) and finally the sub-analysis of the data from a small number of depressed rapid cycling BD patients again suggested that 300mg of quetiapine monotherapy was superior to placebo (Suppes et al., 2010).

It seems that lithium has a week but positive effect (Young et al., 2010) and also there are some positive but equivocal data for valproate (Muzina et al., 2010). On the other hand, the data are clearly negative for paroxetine (McElroy et al., 2010c).

The combination of lithium and divalproex was not effective and the further addition of lamotrigine did not seem to add anything in terms of efficacy (Kemp et al., 2012b)

### 3.e.2. Relapse prevention in rapid cycling patients

For the prevention phase, the data so far suggest that divalproex is not more effective than lithium (Calabrese et al., 2005a) and also that the combination of lithium plus divalproex is not better than lithium alone (Kemp et al., 2009). One small study reported that the combination of lithium plus carbamazepine did better than either agent alone (Denicoff et al., 1997). It is interesting that the data are negative for lamotrigine although in some secondary outcomes there was a beneficial signal especially in BD-II patients (Calabrese et al., 2000). Overall, the widely believed concept among clinicians that divalproex is more effective than lithium in the long-term management of rapid-cycling bipolar disorder was not supported by a trial on 139 patients (Findling et al., 2005).

One post-hoc analysis suggested that aripiprazole was efficacious (Muzina et al., 2008). There are no data on other antipsychotics in monotherapy concerning the maintenance phase. A post hoc analysis reported that rapid cycling patients did less well during the extended observation period than non-rapid cycling patients, regardless of treatment and that overall olanzapine and divalproex appeared comparable (Suppes et al., 2005).

Another study confirmed the efficacy and safety of quetiapine add-on to lithium or divalproex in the prevention of mood episodes in rapid cycling BD-I patients with most recent episode manic/mixed or depressive (Vieta et al., 2008a). There was a North American study with a similar design as the previous one reporting similar results (Suppes et al., 2009). A large controlled trial which evaluated adjunctive maintenance treatment with RLAI on TAU in 240 BD-I patients with at least four mood episodes in the 12 months prior to study entry yielded positive results (Macfadden et al., 2009).

The results of the STEP-BD support a role of antidepressants in the development of rapid cycling in a subpopulation of BD patients (Schneck et al., 2008; Ghaemi et al., 2010). A similar conclusion came from earlier randomized controlled study of rapid cycling patients using a double-blind on-off-on-off design with the use of tricyclic antidepressants (Wehr et al., 1988)

Finally, the data are negative concerning the administration of 6 g/day of ethyl-eicosapentanoate (EPA) as augmentation of treatment with mood stabilizers in rapid cycling patients with bipolar depression (Keck et al., 2006b).

One meta analysis suggested that lithium is at least partially efficacious in rapid cycling patients (Kupka et al., 2003), another one suggested there is no clear advantage of any treatment option vs. the others (Tondo et al., 2003), while a third one proposed that some atypical antipsychotics (especially quetiapine and olanzapine) may be considered as the first-line treatment options (Cruz et al., 2010). The meta-analysis of 20 studies published from 1974-2002 comparing subjects with rapid and non-rapid cycling BD reported that in contrast to common beliefs, lithium prophylaxis has at least partial efficacy in a considerable number of rapid cyclers, especially when

antidepressants are avoided. Hypothyroidism may be associated with mood destabilization in vulnerable patients (Kupka et al., 2003).

### 3.f. Treatment of special conditions

#### 3.f.1. Treatment of comorbid conditions

Comorbidities are common in bipolar patients and often need more elaborated therapeutic interventions (Fountoulakis, 2015e, f, g).

##### 3.f.1.1 Treatment of comorbid substance abuse disorder (SUD)

There are two placebo controlled trials suggesting that the combination of valproate and lithium in BD patients with co-occurring alcohol dependence improves both mood and alcohol use symptoms (Salloum et al., 2005; Salloum et al., 2007) and that lithium treatment in BD adolescents improves mood and substance use symptoms. (Cerullo and Strakowski, 2007). Lithium can be used for the treatment of concomitant substance and polysubstance abuse (Geller et al., 1992; Geller et al., 1998), and quetiapine and risperidone can reduce drug craving (Nejtek et al., 2008). On the contrary, the data concerning quetiapine for alcohol abuse are negative (Brown et al., 2008; Sherwood Brown et al., 2014). For bipolar patients with alcohol dependence, the opiate receptor antagonist naltrexone could be useful (Sherwood Brown et al., 2009), and a preliminary report is positive for acamprosate (Tolliver et al., 2012) but negative concerning the treatment of any substance use with N-acetylcysteine (Bernardo et al., 2009). One trial on the usefulness of citicoline in the treatment of

cocaine use was inconclusive (Brown et al., 2015) as was one study with the use of topiramate in alcohol dependence (Sylvia et al., 2016).

There are open-label medication trials which provide limited support to quetiapine, aripiprazole, bupropion and lamotrigine for the treatment of BD patients with cocaine dependence. Also, aripiprazole might be helpful in patients with alcohol use disorders (Cerullo and Strakowski, 2007; Sepede et al., 2014).

Overall, while some data are available for alcohol, cannabis, and cocaine use comorbid with BD the evidence is sparse concerning heroin, amphetamine, methamphetamine, and polysubstance SUD comorbid with BD (Beaulieu et al., 2012).

### 3.f.1.2 Treatment of comorbid anxiety and disorders

A post hoc analysis of anxiety symptoms with data from 2 RCTs of 8-week duration of quetiapine (300 or 600 mg/day) (Calabrese et al., 2005b; Thase et al., 2006) reported that at endpoint there was no difference between treatment groups and placebo concerning the total HAM-A score, but there was a difference both for the psychic and the somatic anxiety subscale scores in comparison to placebo ($p<0.001$) (Lydiard et al., 2009). Also, quetiapine XR (50-300 mg/day) was superior both to divalproex ER (500-3000 mg/day) and placebo in the improvement of anxiety in BD patients with comorbid panic attacks or generalized anxiety disorder (GAD) (Sheehan et al., 2013). In another study, again quetiapine (300 or 600 mg/day) and paroxetine (20 mg/day) produced a significant improvement in anxiety in terms of change of HAM-A scale score from baseline in acutely depressed BD patients (McElroy et al., 2010c). Of note, quetiapine (300-600 mg/day) also significantly improved the HAM-

D score from baseline while this was not the case with paroxetine (600-1800 mg/day; p=0.279) (Young et al., 2010). However, another study was negative for quetiapine concerning its effect on depression in BD patients with GAD (Gao et al., 2014).

Lurasidone (20-60 mg/day; N=166 or 80-120 mg/day) also significantly improved anxiety symptoms in comparison to placebo (Loebel et al., 2014a).

On the contrary, risperidone monotherapy was not an effective anxiolytic for BD patients with comorbid panic disorder or GAD in doses of 0.5-4 mg/day over 8 weeks of treatment (Sheehan et al., 2009), and similar results were obtained with ziprasidone (Suppes et al., 2014).

The data concerning divalproex (rapidly titrated up to 2500 mg/day, as tolerated, to a target serum level of 50–100 mg/dl) are equivocal because the only positive study was based on a very small study sample (25 outpatients with BD-I depression) (Davis et al., 2005).

It is reasonable to suggest that also benzodiazepines can be used as adjunctive medication for sedation or for the treatment of anxiety although abuse, tolerance and dependence constitute important problems. Although approved for the treatment of GAD, pregabalin has no data in BD. However, again it is reasonable to suggest it might be a useful agent for the treatment of anxiety disorders that commonly accompany BD and could substitute for benzodiazepines. A significant advantage is that it is not metabolized by the liver.

There is one study suggesting that adjunctive topiramate could be beneficial in the treatment of BD with comorbid Obsessive Compulsive disorder (OCD) but the overall design and reporting of results does not permit reliable conclusions (Sahraian et al., 2014).

The ranking of the treatment of comorbid anxiety is shown in table 3.

### 3.f.1.3. Weight gain

Topiramate is not effective in the treatment of BD per se, however it is unique because of its ability to cause weight loss at dosages of 50-200 mg/day. A review reported that more than 70% of patients taking topiramate for a mean duration of 5 months lost a mean of 5-6 kilograms (Arnone, 2005). However topiramate might cause de novo depression and suicidality in some patients, although no completed suicides related to topiramate have been reported (Fountoulakis et al., 2012c).

### 3.f.2. Treatment of Agitation

Probably most clinicians would choose antipsychotics in severely agitated bipolar patients, and this option is supported by a double blind clinical trial which reported that intramuscular haloperidol (5-10 mg) was equal in efficacy but faster acting in comparison to intramuscular clonazepam (1-2 mg) in agitated mania at 0, 30 and 60 minutes (Chouinard et al., 1993). Similarly, intramuscular olanzapine (10 mg, first two injections; 5 mg, third injection) was reported to be superior to lorazepam (2 mg, first two injections; 1 mg, third injection), for the control of agitation in manic patients. Already 2 hours after the first injection, patients treated with olanzapine showed a significantly greater reduction in scores on all agitation scales compared with patients treated with either placebo or lorazepam (Meehan et al., 2001).

Valproate oral loading of 20 mg/kg/day was reported to be comparable to haloperidol 0.2 mg/kg/day for the treatment of exited manic patients in a single blind study and the effect was evident within 3 days from starting (McElroy et al., 1996). Overall,

valproate loading up to 30 mg/kg/day was reported to be safe and well tolerated (Hirschfeld et al., 1999).

Inhaled loxapine exerted an anti-agitation effect at 10 min at both the 5 mg and 10 mg doses and was superior to placebo at all-time points measured. For safety reasons it has been recommended that inhaled loxapine should be restricted to a single dose in 24 h and needs to be subject to a Risk Evaluation and Mitigation Strategy program (Citrome, 2012; Kwentus et al., 2012). In Europe, two doses are allowed (the second must be given 2 hours after the initial inhalation) (Popovic et al., 2015).

The issue of agitation with aripiprazole is controversial. As an adverse event it is not reported in the dataset and on the contrary, aripiprazole is a recommended evidence based treatment against agitation associated with schizophrenia or bipolar mania (Sanford and Scott, 2008; Gonzalez et al., 2013; Citrome et al., 2016). However it has been reported under naturalistic conditions (Di Lorenzo et al., 2007) and especially in vulnerable populations such as elderly patients (Coley et al., 2009). Agitation has also been described when initiating aripiprazole in patients after prolonged treatment with potent D2 blocking agents that may result in an upregulation of postsynaptic dopamine receptors (Lea et al., 2007). However, a major obstacle for a fair estimate of the rate of agitation with aripiprazole is that akathisia can easily be mistaken as agitation (Thomas et al., 2015), especially by less experienced raters.

### 3.f.3. Treatment of neurocognitive deficits

The presence of a significant neurocognitive deficit in BD patients has been solidly shown and it concerns all phases of the disorder, including periods of euthymia (Tsitsipa and Fountoulakis, 2015). Galantamine may have specific benefits for

episodic memory, but not processing speed, in patients with cognitive impairment as part of BD (Ghaemi et al., 2009). One study reported that pramipexole may improve neurocognition in euthymic patients only (Burdick et al., 2012) while the data are negative for N-acetyl cysteine (NAC) (Dean et al., 2012).

Adjunctive intranasal insulin (40 IU q.i.d.; N=34) had a beneficial effect on executive function but not on the other neurocognitive measures in euthymic patients (McIntyre et al., 2012a). Also adjunctive mifepristone, which is a synthetic steroid, at 600 mg/day improved spatial working memory in BD depressed patients, and this was evident also 7 weeks after the cessation of treatment (Watson et al., 2012)

ECT was reported to produce an improvement in neurocognitive function similar to that of algorithm-based pharmacological treatment (Kessler et al., 2014).

### 3.f.4. Suicide

There is much discussion concerning the potential anti-suicidal efficacy of specific drugs and especially of lithium. However almost all the data come from studies of naturalistic and epidemiological nature and no controlled studies exist.

There is only one post-hoc analysis which investigated suicidality in BD-I patients during treatment with olanzapine in combination with lithium or divalproex. In mixed patients with residual suicidality, suicidal thoughts were associated with somatic discomfort, agitated depression, and psychosis. It seems that combination therapy with olanzapine plus lithium (N=36) vs. lithium alone (N=22) significanlty reduced the score in the suicidal item of the HAM-D by 58% vs. 29% ($p<0.05$) within 1 week, and all associated symptoms within 2 weeks by averages of 31% vs. 12% ($p<0.05$) (Houston et al., 2006). The analysis of pharmaco-epidemiological data suggest that

treatment with lithium but not with valproate is associated with lower suicidality (Goodwin et al., 2003; Song et al., 2015).

### 3.g. Non-biological treatment options

There are some but overall limited data concerning the usefulness of specific adjunctive psychotherapies (Reinares et al., 2014; Miziou et al., 2015). Research so far has focused on acute depression and the maintenance phase but not on acute mania. These studies suffer from the same limitations and methodological problems as all psychotherapy trials do. There is no universally accepted standardized method to conduct this kind of studies and blinding and the nature of the control intervention are unresolved limitations. The grading of these treatment options is shown in table 8.

#### 3.g.1. Cognitive-behavioral therapy (CBT)

The overall data for the long-term efficacy of CBT either as monotherapy or as add on to psychoeducation, and in comparison to TAU are negative concerning relapse prevention. However, there are some positive results for the acute depressive phase in BD (Ball et al., 2006; Scott et al., 2006; Zaretsky et al., 2008; Costa et al., 2011; Gomes et al., 2011; Meyer and Hautzinger, 2012; Gonzalez Isasi et al., 2014). A post hoc analysis suggested that CBT could be more effective than TAU in patients with less than 12 previous episodes, but less effective in those with more episodes (Scott et al., 2006). In BD patiens with insomnia, CBT for insomnia was superior to psychoeducation concerning manic relapses (Harvey et al., 2015).

### 3.g.2. Psychoeducation

The data on adjunctive psychoeducation suggest that -in comparison to TAU or to non-specific intervention- it prevents relapse to both poles if administered to patients in clinical remission (Perry et al., 1999; Colom et al., 2003; Colom et al., 2009; Lobban et al., 2010; de Barros et al., 2013) but it has no effect on biological rhythms (Cardoso Tde et al., 2015). Again a post-hoc analysis suggested that patients with more than 7 episodes did not show significant improvement with group psychoeducation for time to recurrence, and those with more than 14 episodes did not benefit from the treatment in terms of time spent ill (Colom et al., 2010). A systematic review confirmed the above (Bond and Anderson, 2015).

### 3.g.3 Interpersonal and social rhythm therapy (IPSRT)

Overall there are no convincing data on the usefulness of IPSRT during the maintenance phase of BD, however there are some data suggesting that if applied early and particularly already during the acute phase, it might prolong the time to relapse (Frank et al., 2005; Frank et al., 2008; Swartz et al., 2012; Inder et al., 2015).

### 3.g.4. Family Focus Treatment (FFT)

Overall the literature supports the idea that interventions which focus on families and caregivers exert a beneficial impact especially on family members, but the effect on the patients themselves is controversial and uncontrolled. Probably it improves issues like treatment adherence and family dynamics (Miklowitz et al., 2000; Miklowitz et

al., 2003; Rea et al., 2003; Reinares et al., 2004; Reinares et al., 2008; D'Souza et al., 2010)

### 3.g.5. Intensive psychosocial intervention

'Intensive' psychotherapy is another option but it is of unknown efficacy with limited research support (Miklowitz et al., 2007b; Miklowitz et al., 2007a). The term refers to up to 30 sessions of CBT, IPSRT, or FFT within 9 months.

### 3.g.6. Cognitive remediation and functional remediation.

The data are positive in improving functioning, which is the critical endpoint, but mostly negative concerning cognitive outcomes when using cognitive remediation techniques as add on to TAU in BD patients (Martinez-Aran et al., 2011; Lahera et al., 2013; Torrent et al., 2013) although a more recent post hoc analysis was promising (Sole et al., 2014).

### 3.g.7. Mindfulness-based interventions (MBCT).

Overall the data do not support a beneficial effect of MBCT on the core symptoms of BD but also suggest that MBCT could be useful in the reduction of anxiety in BD patients. So far there are no data supporting its efficacy in the prevention of recurrences. (Williams et al., 2008; Ives-Deliperi et al., 2013; Perich et al., 2013a; Perich et al., 2013b).

### 3.g.8 Internet-based interventions

There is only one randomized trial which compared a completely Internet-based preventive program for bipolar disorder, adjunctive to usual pharmacological management vs. a control intervention. The results suggested no differences between treatment groups (Barnes et al., 2015). The design of the study precludes deriving general conclusions for the efficacy of web-based approaches. Another study which combined psychoeducation with mobile phone technology did not show any benefit vs. paper and pencil method, however this could mean that a mobile phone approach could be an important alternative without compromising the outcome (Depp et al., 2015).

## 4. Safety issues with pharmacotherapy of BD

A comprehensive grading of all agents in terms of their safety and tolerability profile is shown in table 9.

### 4.a. Lithium

Lithium has a narrow therapeutic window concerning its dosage and plasma levels (recommended plasma level 0.6-1.2 mmol/L), and laboratory testing and thorough investigation before starting lithium treatment (ECG; kidney function etc.) is necessary. Unfortunately this often delays the initiation of treatment. Adverse events are more frequent with higher doses, while ‘rebound mania’ has been described upon withdrawal. The most frequent adverse events include neurological, endocrinological

(more often from the thyroid), cardiovascular, renal, gastrointestinal, hematological and dermatological manifestations, and lithium intoxication is not rare. In clinical practice patients often complain of sedation, tremor and sometimes a decline in creative thinking (Shaw et al., 1986; Engelsmann et al., 1988; Stoll et al., 1996). A general negative impact of lithium on neurocognitive function has been reported (Karniol et al., 1978; Kropf and Muller-Oerlinghausen, 1979; Reus et al., 1979; Squire et al., 1980; Connelly et al., 1982; Lund et al., 1982; Shaw et al., 1987; Engelsmann et al., 1988; Maarbjerg et al., 1988; Kocsis et al., 1993; Kessing, 1998; Honig et al., 1999; Bora et al., 2007; Senturk et al., 2007; Goldberg, 2008). It seems that there is a complex relationship between lithium treatment, female gender, hypothyroidism and rapid cycling (Cowdry et al., 1983; Bauer and Whybrow, 1990; Bauer et al., 1990; Gyulai et al., 2003a; Fountoulakis et al., 2008b). While most authors argue that lithium is neuroprotective, a neurotoxic effect is also possible in the long term, even at therapeutic levels, especially in combination with antipsychotics (Fountoulakis et al., 2008b). Comprehensive guidelines concerning lithium treatment and optimal therapeutic serum levels are available and should be applied (Malhi et al., 2011), and a recent review provides up-to-date information on its safety (Murru et al., 2015).

**4.b Antiepileptics**

The recommended therapeutic valproate serum concentration is 50-150 mg/mL. It is not recommended to be used in women of childbearing age, due to the high frequency of unplanned pregnancies in bipolar females, and the relatively high teratogenicity of valproate. Other potential acute side effects are weight gain and hair loss. Its use has

been associated with polycystic ovary syndrome (PCOS). It is to be noted however, that similar to epilepsy, there is an association between PCOS and major psychiatric disorders, including BD. An increased risk can also be demonstrated in their siblings suggestive of shared familial factors between PCOS and psychiatric disorders (Cesta et al., 2016).

The typical dosage of carbamazepine in the treatment of acute mania is 600-1800 mg/day (serum concentration 4-12 mg/mL). After several weeks under carbamazepine, an induction of hepatic enzymes (CYP 3A4) occurs, the drug levels drop and may require additional upward dose titration (Bertilsson and Tomson, 1986). The dosage-related adverse effects include double or blurred vision, dizziness, sedation, ataxia, vertigo, gastrointestinal disturbances, cognitive impairment, hematological effects and Stevens-Johnson syndrome including its related dermatologic effects (Tohen et al., 1991; Tohen et al., 1995; Blackburn et al., 1998).

The most significant drawback of lamotrigine treatment is the need to initiate it at 25 mg/day for two weeks, then 50 mg/day for another two weeks and then by increments of 25-50 mg/day thereafter to avoid a moderately high incidence of rash (Seo et al., 2010)

Carbamazepine decreases lamotrigine concentrations by approximately 50%, and in combination therapy, lamotrigine can be started with higher dosages and faster titration. Vice versa, when combined with valproate a slower titration scheme is needed for lamotrigine., Carbamazepine induces the metabolism of other agents as well, e.g., risperidone (Ono et al., 2002).

It is also important to note the adverse effects of topiramate because although it is not used in the treatment of BD per se, it is often administered in BD patients in order to lose weight or to treat a comorbid substance abuse disorder. It is reported that

topiramate impairs attention, verbal memory, psychomotor speed, and word-finding even at very low dosages (25-50 mg/day). This impairment is reversible after discontinuation of the drug (Salinsky et al., 2005; Goldberg, 2008).

An important recent development was the safety warning by the FDA after a meta analysis which suggested that antiepileptics might double the suicidal risk (FDA, 2008). The field remains uncertain, with some reports and authors supporting the FDA warning (Nilsson et al., 2002; Mula and Sander, 2007; Gibbons et al., 2009; Andersohn et al., 2010; Arana et al., 2010; Olesen et al., 2010; Patorno et al., 2010; VanCott et al., 2010; Ziemba et al., 2010; Wen et al., 2011; Fountoulakis et al., 2012c; Pugh et al., 2012; Siamouli et al., 2014). It is important to note that suicidality data came from the registration of adverse events rather than from systematically collected data (Hesdorffer and Kanner, 2009). However, it seems clear that topiramate, lamotrigine and levetiracetam are related to increased suicidality in non-psychiatric patients and this should be the focus of further research.

**4.c. Antipsychotics**

The adverse effects of FGAs include EPS, tardive dyskinesia and hyperprolactinaemia and the life-threatening but rather rare neuroleptic malignant syndrome, while the most frequent side effects of chlorpromazine are EPS, tardive dyskinesia, postural hypotension and hepatotoxicity.

On the other hand, the most significant problem with some of the second generation antipsychotics (SGAs) is weight gain, hyperlipidaemia and diabetes mellitus. The treatment of these somatic conditions is difficult and the methods proposed have produced rather unsatisfactory results so far. Hyperprolactinaemia and EPS are the

most frequent adverse effects with amisulpride. Akathisia and EPS are the adverse effects most often reported with aripiprazole.

Concerning olanzapine, the most frequent adverse effects include dry mouth, weight gain, increased appetite, diabetes mellitus and metabolic syndrome and somnolence. The main adverse effects of quetiapine are persistent sedation and weight gain, however, to a lower extent than olanzapine. Maybe the XR formulation of quetiapine induces less sedation in comparison to the IR formulation (Riesenberg et al., 2012). The main side effects of risperidone are dose-related EPS, weight gain, sedation and hyperprolactinemia. Somnolence, akathisia and EPS, as well as a significant QTc prolongation are the main adverse effects of ziprasidone treatment, however ziprasidone is not associated with the metabolic syndrome (Kemp et al., 2012a)

Reports on antipsychotics concerning adverse effects on neurocognition are rare and conflicting (Holmes et al., 2008; Goldberg and Chengappa, 2009; Pan et al., 2011). There are data suggesting that an executive function deficit is correlated with years of exposure to antipsychotic drugs (Zubieta et al., 2001). This latter finding could reflect either the toxic effect of chronic psychosis, the toxic effect of long term medication or both. Current antipsychotic treatment in BD patients is reported to relate to worse performance in sustained attention and visuomotor speed, across all executive function tests as well as in semantic fluency, verbal learning and recognition memory, even when studies were controlled for differences in clinical features (King, 1994; Altshuler et al., 2004; Frangou et al., 2005; Jamrozinski et al., 2009).

### 4.d. Antidepressants

There is a number of different adverse effects caused by antidepressants. Most of them are not severe, may cause significant burden to the patients but usually improve with time (NHS, 2014).

The adverse effects of SSRIs and serotonin and norepinephrine re-uptake inhibitors (SNRIs) include agitation, shakiness, anxiety or feeling of being sick, indigestion, stomach aches, diarrhoea or constipation, loss of appetite, dizziness, insomnia and other sleep disorders, or, on the contrary, hypersomnia and sedation, headache, loss of libido, weight gain, excessive sweating, hyponatriaemia (especially in the elderly) and sexual dysfunction. The adverse effects of tricyclic antidepressants (TCAs) include: dry mouth, blurred vision, constipation, dysuria, drowsiness, dizziness, weight gain, excessive sweating and heart rhythm problems. A rare but potentially life-threatening adverse event is the serotonin syndrome whose symptoms include confusion, agitation, muscle twitching, sweating, shivering and diarrhoea. Rare, but serious cases may manifest with very high fever, epileptic fits, arrhythmia and coma. All classes of antidepressants have been linked to an increased risk of developing type 2 diabetes, but the causality is uncertain.

There is a warning issued by the FDA (black box warning) concerning the risk of suicidality in pediatric patients taking SSRIs for depression (Libby et al., 2007) and a number of papers suggest that antidepressants are related to an increased risk for suicidal behaviour (Rouillon et al., 1991; Khan et al., 2000; Khan et al., 2001; Luoma et al., 2002; Baldessarini et al., 2003a; Healy, 2003; Khan et al., 2003) but not for completed suicide (Whittington et al., 2004). This might constitute one of the most interesting paradox of our contemporary psychiatry since antidepressants prevent

suicidal behaviour among severely ill, frequently suicidal 'real life' unipolar depressives but may provoke such behaviour sometimes in less severe, actually nonsuicidal unipolar depressives (Leon et al., 1999; Angst et al., 2002; Yerevanian et al., 2004; Simon et al., 2006; Gibbons et al., 2007). It has been suggested that antidepressants induce suicidality essentially only in pseudo-unipolar patients (Akiskal and Benazzi, 2005; Rihmer and Akiskal, 2006; Perlis et al., 2007b) while the data from the STAR*D trial suggest the presence of a genetic vulnerability predisposing to the manifestation of new suicidal ideation after antidepressant treatment (Laje et al., 2007; Perlis et al., 2007b; Perlis et al., 2007a).

**4.e. Switching to the opposite pole**

It is widely accepted among psychiatrists that both antidepressants and FGAs can induce a mood switch to the opposite pole, or a chronic, dysphoric, mixed or irritable state in BD patients and may accelerate episode frequency and/or may cause other forms of course destabilization in patients with BD. However, hard evidence is limited and the bulk of evidence comes from chart reviews and retrospective and open studies. A comprehensive summary of the risk to induce switching for all agents during the three phases of treatment is shown in table 10

The literature suggests that without the concomitant use of an antimanic agent the switch rate to mania or hypomania is around 20-40% (Bottlender et al., 2001; Goldberg and Truman, 2003; Bottlender et al., 2004) while with the concomintant use of an antimanic agent the rate is reduced to 14% or below (Nemeroff et al., 2001; Post et al., 2001; Post et al., 2006; Harel and Levkovitz, 2008; Licht et al., 2008; Tondo et al., 2010). More recent reports suggests that switching is exclusively related

to antidepressant monotherapy while the concomitant use of an antimanic agent has a robust protective effect (Viktorin et al., 2014). The results of the STEP-BD support the potentially harmful role of antidepressants in the long-term course of BD (Truman et al., 2007; El-Mallakh et al., 2008; El-Mallakh et al., 2015). According to that study switching to the opposite pole was not dose-dependent (Tada et al., 2015). However a number of larger RCTs reported negative data concerning switching with paroxetine and bupropion (Sachs et al., 2007), fluoxetine, even as monotherapy in BD-II patients (Amsterdam et al., 2004), and citalopram (Schaffer et al., 2006). There are some data suggesting a higher risk of switching while on treatment with venlafaxine (Amsterdam and Garcia-Espana, 2000; Vieta et al., 2002; Altshuler et al., 2006; Leverich et al., 2006; Post et al., 2006; Altshuler et al., 2009) and imipramine (Himmelhoch et al., 1991; Nemeroff et al., 2001; Silverstone, 2001), but a more recent study reported that venlafaxine was equal to lithium and without any increase in the switch rate (Lorenzo-Luaces et al., 2016).

It is important to mention that switching to mania or hypomania during treatment of comorbid OCD (White et al., 1986; Steiner, 1991; Vieta and Bernardo, 1992; Rihmer et al., 1996; Perugi et al., 2002) or panic disorder with antidepressants have been reported (Pecknold and Fleury, 1986; Sholomskas, 1990).

The switch risk is probably as high as 18.2% in the short term and 35.6% during the continuation phase (Post et al., 2003) and is higher in BD-I patients in comparison to BD-II (14.2% vs. 7.1% in acute trials and 23.4% vs. 13.9% in maintenance studies). The rates of switching in unipolar patients are lower than those of bipolar (1.5% in acute trials and 6.0% in maintenance studies) (Bond et al., 2008; Tondo et al., 2010).

Haloperidol and perphenazine treatment have been associated with the development of dysphoria and depression although the data are inconclusive for haloperidol (Tohen

et al., 2003b; Zarate and Tohen, 2004). On the contrary, SGAs do not appear to induce depression while some authors suggest they possess a mild protective property against switching (Tohen et al., 2003c; Amsterdam and Shults, 2005a; Calabrese et al., 2005b; Keck et al., 2005; Thase et al., 2006; Benazzi et al., 2009). A recent meta-analysis reported that treating acute mania with SGAs is associated with a 42% lower risk of switch to depression than with haloperidol. Nevertheless, caution should be taken when considering this to be a class effect, as only olanzapine, quetiapine, and ziprasidone may show these advantages (Goikolea et al., 2013b).

Overall there are no data to suggest a generalized and class effect for antidepressants or FGAs concerning the induction of an affective switch. There are negative data concerning all SSRIs and SGAs studied and positive data only concerning venlafaxine, imipramine and perphenazine. Some authors believe that at least, the switch risk, and perhaps also the risk for rapid cycling and new-onset suicidality have been over-interpreted (Grunze, 2008) and thus the issue of switching is still open and further research is needed. Also negative for the presence of a treatment-induced switch are the longitudinal data of Jules Angst (Angst, 1985). For a safe use of antidepressants in bipolar disorder, clinicians may follow the recommendations of the International Society for Bipolar Disorders Task Force (Pacchiarotti et al., 2013).

## 5. Review of existing guidelines for BD

A number of treatment guidelines were identified and their reference lists were utilized (APA, 1994, 1995; Suppes et al., 1995; Frances et al., 1996; 1997; AACAP, 1997; Goodwin et al., 1997; Jobson, 1997; Kusumakar et al., 1997; McClellan and

Werry, 1997; Gilbert et al., 1998; Barreira et al., 1999; Bauer et al., 1999b; Rush et al., 1999; Dennehy, 2000; Goldberg, 2000; Sachs et al., 2000; Allen et al., 2001; Montgomery, 2001; Suppes et al., 2001; APA, 2002; Grunze et al., 2002; Suppes et al., 2002; Goodwin, 2003; Grunze et al., 2003; Licht et al., 2003; Rush et al., 2003; Suppes et al., 2003; Grunze et al., 2004; Hirschfeld, 2005; Yatham et al., 2005; National Collaborating Centre for Mental Health, 2006; O'Dowd, 2006; Yatham et al., 2006; 2008; Nolen et al., 2008; Goodwin, 2009; Grunze et al., 2009; Jon et al., 2009; Ng et al., 2009; Yatham et al., 2009; Grunze et al., 2010; 2011; Beaulieu et al., 2012; Bond et al., 2012; McIntyre et al., 2012b; Rosenbluth et al., 2012; Schaffer et al., 2012; Grunze et al., 2013; Yatham et al., 2013b; Yatham et al., 2013c; Mohammad and Osser, 2014; Malhi et al., 2015; Ostacher et al., 2015a; Woo et al., 2015; Goodwin et al., 2016). An additional source was the National Institute of Clinical Excellence (NICE) guideline concerning BD (NICE, 2014), while the latest version of the guidelines of the British Association of Psychopharmacology (Goodwin et al., 2016) were included although they were published after the date of last literature search.

A description of the most important and most recent guidelines (after 2005) will be included in the text that follows. In tables 17, 21 and 25 there is a detailed description of difference between the current CINP guidelines and previously developed guidelines by other bodies.

### 5.1. American Psychiatric Association Treatment Guidelines for BD

In 2008 the APA developed a draft of new guidelines after a thorough review of the literature. However they were never published because of unresolved issues pertaining to the conflict of interest.

### 5.2. The Canadian Network for Mood and Anxiety Treatments and International Society on Bipolar Disorder guidelines (CANMAT/ISBD)

The most recent 2013 version of the CANMAT/ISBD guidelines (Yatham et al., 2013c) suggest that for the treatment of acute manic episodes the first line recommendation is monotherapy with lithium, divalproex, divalproex ER, olanzapine, risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, asenapine or paliperidone ER and adjunctive therapy with risperidone, quetiapine, olanzapine, aripiprazole, asenapine on lithium or divalproex. The second line includes monotherapy with carbamazepine, carbamazepine ER, ECT or haloperidol and combination therapy with lithium plus divalproex. The third line of treatment includes monotherapy with chlorpromazine, clozapine, oxcarbazepine, tamoxifen or cariprazine and combination therapy with lithium or divalproex plus haloperidol, lithium plus carbamazepine or adjunctive tamoxifen. They do not recommend monotherapy with gabapentin, topiramate, lamotrigine, verapamil, tiagabine and combination therapy with risperidone or olanzapine plus carbamazepine.

For the treatment of acute BD-I depression as first line option they recommend monotherapy with lithium, lamotrigine, quetiapine or quetiapine XR and combination therapy with lithium or divalproex or olanzapine plus an SSRI, lithium plus

divalproex and lithium or divalproex plus bupropion. The second line includes monotherapy with divalproex or lurasidone and combination therapy with quetiapine plus an SSRI, adjunctive modafinil and lithium or divalproex plus lamotrigine or lurasidone. The third line includes monotherapy with carbamazepine, olanzapine or ECT or combination therapy with lithium plus carbamazepine or pramipexole, lithium or divalproex plus venlafaxine, lithium plus MAOI, lithium or divalproex or atypical antipsychotic plus a TCA, lithium or divalproex or carbamazepine plus an SSRI plus lamotrigine and quetiapine plus lamotrigine. They do not recommend monotherapy with gabapentin, aripiprazole or ziprasidone and combination therapy with adjunctive ziprasidone or levetiracetam.

For the maintenance treatment, the first line recommendation includes monotherapy with lithium, lamotrigine, divalproex, olanzapine, quetiapine, risperidone LAI and aripiprazole and adjunctive therapy with quetiapine, risperidone LAI, aripiprazole or ziprasidone on lithium or divalproex. The second line monotherapy includes carbamazepine and paliperidone ER and combination therapy with lithium plus divalproex or carbamazepine, lithium or divalproex plus olanzapine, risperidone or lamotrigine and olanzapine plus fluoxetine. The third line monotherapy includes asenapine and the adjunctive therapy includes phenytoin, clozapine, ECT, topiramate, omega-3-fatty acids, oxcarbazepine, gabapentin and asenapine. They do not recommend monotherapy with gabapentin, topiramate, or antidepressants and adjunctive therapy with flupenthixol.

### 5.3. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of BD.

The latest WFSBP guidelines utilized a modified version of the PORT method to grade the data concerning efficacy (Grunze et al., 2009; Grunze et al., 2010, 2013) and afterwards utilized a secondary classification to include also safety and tolerability.

For the treatment of acute mania, as first choice agents are ranked aripiprazole, valproate, risperidone and ziprasidone. As second choice olanzapine, quetiapine, asenapine, carbamazepine, haloperidol, and lithium were recommended. The third choice includes chlorpromazine, paliperidone, phenytoin, pimozide and tamoxifen. The fourth includes amisulpride, clonazepam, clozapine, levetiracetam, lorazepam, nimodipine, oxcarbazepine, retigabine, zonisamide, zotepine and ECT. The fifth and final choice includes verapamil. With the utilization of this classification, the WFSBP suggests that concerning the treatment of acute mania the first step includes monotherapy with first choice agents. The second step would be the switching to another first choice agent or combine two first choice agents. Similarly the third step includes combination of two first choice agents. The fourth and fifth steps include combinations of agents essentially according to the judgement of the therapist.

For the treatment of acute bipolar depression, the WFSBP guidelines suggest that first choice agent is only quetiapine while there next best option includes olanzapine, fluoxetine, lamotrigine, valproate, OFC, lithium plus lamotrigine, adjunctive modafinil, N-acetylcysteine on lithium or valproate and FEWP plus carbamazepine. A variety of combinations are proposed as next steps.

For the treatment during the maintenance phase the guidance is more complex and on the basis of the available data the WFSBP guidelines suggest the use of aripiprazole, lamotrigine, lithium, quetiapine, olanzapine and risperidone but they note that not all of them prevent both mania and depression. They also note the problems because of the metabolic syndrome induced by some of these agents when used for prolonged periods of time. They also suggest the avoidance of typical antipsychotics because of the risk to induce tardive dyskinesia.

### 5.4. British Association for Psychopharmacology (BAP)

The 2016 BAP guidelines for the treatment of BD (Goodwin et al., 2016) recommend for acute mania antidopaminergic agents, lithium or valproate. For acute bipolar depression they recommend quetiapine, olanzapine, olanzapine plus fluoxetine, antidepressants, lurasidone and lamotrigine as combination. It also recommends family focused therapy, IPSRT and CBT as add-on to medication but also CBT as monotherapy as an extrapolation of unipolar depression studies. For the maintenance phase they recommend lithium (for mania, depression and suicide), dopamine antagonists and partial agonists as well as valproate (mainly for mania), lamotrigine (for depression) and Family focused therapy, CBT and IPSRT as add-on to medication

**5.5. The UK National Institute of Clinical Excellence (NICE) treatment guidelines for BD** (NICE, 2014).

Concerning acute mania, the 2014 NICE guidelines recommend the use of olanzapine, risperidone, quetiapine or haloperidol. If the patient does not respond it is recommended to change to another antipsychotic and the choice should be made also on the basis of previous response if it exists. If the patient is already under treatment with lithium or valproate then the recommendation is to increase dosage to the highest permitted and reassessment should follow before the changing of medication. If an antidepressant is in place, it should be discontinued. The second step includes combination of lithium or valproate plus an antipsychotic and the third step demands hospitalization. The NICE warns against the use of gabapentin, lamotrigine and topiramate in acute mania.

For acute bipolar depression, the NICE recommends olanzapine, OFC, quetiapine, lamotrigine, lithium and valproate. If the patient is already under treatment with lithium or valproate then the recommendation is to increase the dosage to the highest permitted and reassessment should follow before the changing of medication. The next step includes combination of lithium or valproate plus quetiapine or OFC. The third step includes lithium plus lamotrigine or olanzapine and valproate plus lamotrigine. The NICE warns against the use of gabapentin and topiramate.

During the maintenance phase, the NICE guidelines recommend as first line treatment the continuation of the treatment the patient received during the acute phase and led to the resolution of the symptoms. Irrespective of predominant polarity the continuation of this treatment should be done for at least 3-6 months. In case the patient does not wish to follow this, it is recommended to change treatment to lithium, olanzapine,

quetiapine, valproate or lithium plus valproate. Again, NICE warns against the use of gabapentin and topiramate.

The procedure and the interpretation of evidence as presented in the NICE guidelines have been criticized (Jauhar et al., 2016).

## 6. Efficay, recommendation level and precise treatment algorithm

The detailed table of the efficacy level for all treatment options during all phases and against specific features of BD is shown in webappendix 1. The detailed table of the recommendation level for all treatment options during all phases and against specific features of BD is shown in webappendix 2. Add-on and combination data were merged for the sake of simplicity. Additionally, the detailed precise algorithm which was developed is shown in webappendix 3.

The levels of recommendation concerning monotherapy in acute mania and recommended dosages for medication options are shown in table 11, while the recommendation levels for combination treatment are shown in table 12. Recommendation levels concerning treatment options for rapid cycling patients are shown in table 13 and the effects on concomitant depressive and psychotic features are shown in table 14. The recommendation levels for monotherapy and combination treatment in patients with a DSM-IV-TR mixed episode and the specific effects on the manic and the depressive component are shown in table 15 (provided here for academic reasons).

The chart of the algorithm for acute mania/hypomania on the basis of strict evidence and by taking into consideration specific clinical features is shown in table 16. The

comparison of this algorithm to previously developed guidelines for acute mania is shown in table 17.

The levels of recommendation concerning monotherapy in acute bipolar depression, in comorbid conditions and rapid cycling patients and recommended dosages for medication options are shown in table 18, while the levels of recommendation concerning combination treatment are shown in table 19.

The chart of the algorithm for acute bipolar depression is shown in table 20. The comparison of this algorithm to previously developed guidelines for acute bipolar depression is shown in table 21.

The levels of recommendation concerning monotherapy during the maintenance phase and in relationship to index episode, composition of the sample, presence of rapid cycling and the efficacy in the prevention of manic, mixed or depressive episodes as well as recommended dosages are shown in table 22, while the levels of recommendation concerning combination treatment during the maintenance phase are shown in table 23.

The chart of the algorithm for the maintenance phase is shown in table 24. The comparison of this algorithm to previously developed guidelines for the maintenance phase is shown in table 25.

Overall the algorithm consists of the stepwise approach in tables 16, 20 and 24 and in web appendix 3. However, a more fundamental approach would be to utilize web appendix 2 which includes a table with the recommendation levels by clinical indication for all the treatment options. The utilization of this table could be more precise and accurate in comparison to the stepwise description. Until then, the clinician can handle the table in a manual way. First he should decide on the phase of the disorder (acute manic vs. mixed vs. depressive episode vs. maintenance phase).

Then he should choose the combination of the clinical features under the specific phase and finally he will identify which treatment options best fit the clinical syndrome. For example if the patient is in an acute manic episode with some accompanying depressive symptoms (mixed features) and psychotic symptoms and his history suggests he is also a rapid cycling, then the only agents which treats all these conditions are olanzapine and quetiapine followed by lithium which is second choice. If the patient is BD-II in a depressive episode with anxiety, then the only suitable agent is quetiapine. Of course such an algorithm might be too restrictive; however, the clinician can use the table to produce combinations of treatment options to satisfy all clinical needs on the basis on research data.

## 7. Discussion

The current paper represents a systematic search of the literature on the treatment of BD. By using an established approach we identified all relevant RCTs pertaining all faces and special issues of BD and graded the data according to a pre-determined method. Finally, a recommendation level was assigned to all treatment options depending on the clinical situation.

It was interesting to see that except of rare cases, the concept of 'mood stabilizers' is not supported by the available data, especially for those agents traditionally considered as such.

It is obvious that, by far, the body of evidence originates from RCTs which were conducted with agents which have been launched in the last two decades. This constitutes a significant bias in the literature and one should be cautious in the way

that the accumulated clinical experience concerning those agents and treatment modalities with poor evidence based support should also be taken into account.

A low grade of evidence for these old and poorly studied agents and modalities (e.g carbamazepine, clozapine, ECT etc.) does not necessarily mean a lower effectiveness and safety in comparison with other drugs, but it still implies that the clinicians should be cautious in their application in patients with BD. On the other hand it is irrational to use different standards; on the one hand to study carefully and seek flaws in the design of major RCTs and on the other hand to accept a wide recommendation of agents with poor evidence based support because of historical reasons. The authors of the current paper spend much time and effort to grade the agents on the basis of quantitative but also qualitative characteristics of the data available. This effort resulted in the development of a precise algorithm on the basis of a reproducible methodology.

Also, the results on those areas of interest which are not targeted as primary outcomes are reported in a non-systematic way and therefore the grading of evidence is lower. Unfortunately these areas constitute the overwhelming clinical picture of BD.

As with many other guidelines, the inherent limitations of the literature as well as the unavoidable subjectivity of experts when making a recommendation (even when based on evidence) should be taken seriously into consideration by the clinicians when reading the current paper. Also negative results (level 5) should be taken very seriously into consideration, as they should be considered to be scientifically stronger in comparison to positive ones.

Further limitations include the heterogeneity of the RCTs that served as basis for the recommendations and the lack of trials assessing specific subpopulations, following the rules of stratified medicine (Schumann et al., 2014), or applying staging methods

to psychopharmacology (Grande et al., 2015), in search of more precision when treating individual patients (Vieta, 2015). However, these CINP guidelines represent the most up-to-date effort to condense the current knowledge on the management of bipolar disorder from an international perspective.

## 8. Conflict of interest

KNF has received grants and served as consultant, advisor or CME speaker for the following entities: AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Pfizer, the Pfizer Foundation, Sanofi-Aventis, Servier, Shire and others

EV has received grants and served as consultant, advisor or CME speaker for the following entities: Allergan, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lilly, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), the Seventh European Framework Programme (ENBREC), and the Stanley Medical Research Institute.

AHY is employed by King's College London; is Honorary Consultant SLaM (NHS UK); has paid lectures by and participated in advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders; no share holdings in pharmaceutical companies. He was lead Investigator for Embolden Study (AZ), BCI Neuroplasticity study and Aripiprazole Mania Study, investigator initiated

studies from AZ, Eli Lilly, Lundbeck, Wyeth and has received grant funding (past and present): NIHR-BRC (UK); NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK).

HG within the last 3 years received grant/research support from Grant support: NIHR UK, MRC UK, NTW NHS Foundation Trust. Receipt of honoraria or consultation fees: Gedeon-Richter, Lundbeck, Hofmann-LaRoche. Participation in a company sponsored speaker's bureau: BMS, Ferrer, Janssen-Cilag, Otsuka, Lundbeck, Pfizer

LY has been on speaker/advisory boards for, or has received research grants from Alkermes, Allergan, AstraZeneca, Bristol Myers Squibb, CANMAT, CIHR, Eli Lilly, Forest, GlaxoSmithKline, Intas, Janssen, the Michael Smith Foundation for Health Research, Pfizer, Servier, Sumitomo Dainippon, Sunovion, and the Stanley Foundation.

SK within the last 3 years received grants/research support, consulting fees and honoraria within the last three years from Angelini, AOP Orphan Pharmaceuticals AG, AstraZeneca, Eli Lilly, Janssen, KRKA-Pharma, Lundbeck, Neuraxpharm, Pfizer, Pierre Fabre, Schwabe and Servier

HJM received honoraria for lectures or for advisory activities or received grants by the following pharmaceutical companies:, Lundbeck, Servier, Schwabe and Bayer. He

was president or in the Executive Board of the following organisations: CINP, ECNP, WFSBP, EPA and chairman of the WPA-section on Pharmacopsychiatry.

PB has received research grants, honoraria for participation in advisory boards and/or gave presentations from: Allergan, Astra Zeneca, Bristol Myers Squibb, Canadian Institute for Health Research, Eli Lilly, Lundbeck, Janssen, Ontario Brain Institute, Meda-Valeant, Merck, Otsuka, Pierre Fabre Medicaments, Pfizer, Shire, Sunovion, Takeda

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**Figure 1:** PRISMA flowchart for RCTs literature search

**Figure 1:** PRISMA flowchart for treatment guidelines literature search

| | |
|---|---|
| **Grading on basis of efficacy** | |
| **Level 1** | Good research-based evidence, supported by at least 2 placebo controlled studies of sufficient magnitude and good quality. In case of the presence of negative RCTs, positive RCTs should outnumber negative ones |
| **Level 2** | Fair research-based evidence, from one randomised, double-blind placebo controlled trial.<br>Also in case one or more trials exist, however, they fail to fulfil all the criteria above (e.g., very small sample size or no placebo control) as well as in case of positive meta-analysis alone. |
| **Level 3** | Some evidence from comparative studies without placebo arm or from post-hoc analyses. |
| **Level 4** | Inconclusive data or poor quality of RCTs |
| **Level 5** | Negative data |
| **Grading on the basis of safety and tolerability** | |
| **Level 1** | Very good tolerability, few side effects which are not enduring, they do not cause significant distress and are not life-threatening and they do not compromise the overall somatic health of the patient |
| **Level 2** | Moderate tolerability, many side effects which could be enduring, and cause significant distress but they are not life-threatening although they could compromise the overall somatic health of the patient.<br>Agents with very good overall tolerability but with rare life-threatening adverse events, could be classified here only if the lethality risk can be essentially considered to be negligible with the application of procedures and protocols (e.g. laboratory testing, titration schedules etc.) |
| **Level 3** | Poor tolerability, many side effects which are enduring, cause significant distress, compromise the overall somatic health of the patient or are life-threatening.<br>Agents with moderate overall tolerability and rare life-threatening adverse events should be classified here even in cases the lethality risk can be essentially considered to be negligible with the application of procedures and protocols (e.g. laboratory testing, titration schedules etc.) |
| **Recommendations for treatment (combination of efficacy and safety/tolerability)** | |
| **Level 1** | Level 1 or 2 for efficacy and 1 for safety/tolerability |
| **Level 2** | Level 1 or 2 for efficacy and 2 for safety/tolerability |
| **Level 3** | Level 3 for efficacy and 1 or 2 for safety/tolerability |
| **Level 4** | Level 4 for efficacy or 3 for safety/tolerability |
| **Level 5** | Level 5 for efficacy (not recommended) |

**Table 1:** The method for the grading of data, on the basis of efficacy and tolerability.

| | Acute manic episodes | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Agent/modality (alphabetical order)** | **Effect start day** | **Monotherapy** | | | | | **Combination with:** | | | | | |
| | | **overall** | **Core manic** | **Depressive** | **Psychotic** | **agitation** | **MS** | **Cbz** | **Lam** | **Li** | **Val** | **FGAs** |
| **Allopurinol** | - | - | - | - | - | - | 5 | - | - | 3 | - | 5 |
| **Aripiprazole** | 2-4 | 1 | - | 5 | 3 | - | 2 | - | - | - | - | - |
| **Asenapine** | 2 | 1 | - | 4 | - | - | 2 | - | - | - | - | - |
| **Carbamazepine** | 14 | 1 | - | 5 | - | - | - | - | - | - | - | - |
| **Cariprazine** | 4 | 1 | 3 | 5 | - | - | - | - | - | - | - | - |
| **Celecoxib** | - | - | - | - | - | - | - | - | - | - | 2 | - |
| **Chlorpromazine** | - | 4 | - | - | - | - | - | - | - | - | - | - |
| **Clozapine** | - | - | - | - | - | - | - | - | - | - | - | - |
| **ECT** | - | 3 | - | - | - | - | - | - | - | - | - | - |
| **Eslicarbazepine** | - | 5 | - | - | - | - | - | - | - | - | - | - |
| **Gabapentin** | - | 5 | - | - | - | - | 5 | - | - | - | - | - |
| **Haloperidol** | 4 | 1 | 5 | 5 | 3 | 3 | 2 | 2 | - | 2 | 2 | - |
| **Lamotrigine** | - | 5 | - | - | - | - | - | - | - | - | - | - |
| **Levetiracetam** | - | - | - | - | - | - | - | - | - | - | - | - |
| **Licarbazepine** | - | 5 | - | - | - | - | - | - | - | - | - | - |
| **Lithium** | 7 | 1 | 4 | 5 | 2 | - | - | 2 | - | - | - | - |
| **Loxapine inhalant** | - | - | - | - | - | 2 | - | - | - | - | - | - |
| Medroxyprogesterone | - | - | - | - | - | - | 5 | - | - | - | - | - |
| **Olanzapine** | 2-7 | 1 | 3 | 3 | 3 | 2 | 1 | 5 | - | - | 1 | - |
| **Oxcarbazepine** | - | 4 | - | - | - | - | - | - | - | 4 | - | - |
| **Paliperidone** | 2 | 1 | - | - | - | - | 5 | - | - | - | - | - |
| **Pimozide** | - | 4 | - | - | - | - | - | - | - | - | - | - |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Quetiapine** | 4 | 1 | - | 3 | 3 | - | 3 | - | - | 2 | - | - |
| **Risperidone** | 3 | 1 | - | 3 | 3 | - | 3 | - | - | - | 5 | - |
| **Tamoxifen** | 5 | 2 | 3 | 5 | 3 | - | 2 | - | - | 2 | - | - |
| **TMS** | - | 5 | - | - | - | - | - | - | - | - | - | - |
| **Topiramate** | - | 5 | - | - | - | - | 5 | - | - | - | - | - |
| **Valproate** | 5-15 | 1 | 5 | 5 | - | 3 | - | - | - | - | - | 2 |
| **Verapamil** | - | 5 | - | - | - | - | - | - | - | - | - | - |
| **Ziprasidone** | 2 | 1 | 3 | 5 | 3 | - | 5 | - | - | - | - | - |

**Table 2**: Acute mania/mixed treatment phase, grading on basis of efficacy (treatment phase up to 12 weeks). The treatment options are rated according to the rating system shown in table 1

- : no data

Cbz: Carbamazepine

ECT: Electroconvulsive therapy

FGAs: First Generation Antipsychotics

Lam: Lamotrigine

Li: Lithium

MS: Mood Stabilizer

TMS: Transcranial Magnetic Stimulation

Val: Valproate

| | Monotherapy | | | | combination | | | | | Anxiety |
|---|---|---|---|---|---|---|---|---|---|---|
| **agent/modality (alphabetical order)** | **overall** | **BD-I** | **BD-II** | **depressive core** | **MS** | **Cbz** | **Lam** | **Li** | **Val** | |
| **Agomelatine** | - | - | - | - | 5 | - | - | 5 | 5 | - |
| **Aripiprazole** | 3 | 3 | - | - | - | - | - | 5 | - | - |
| **Armodafinil** | - | - | - | - | 4 | - | - | - | - | - |
| **Bupropion** | - | - | - | - | 5 | - | - | - | - | - |
| **Carbamazepine** | 3 | - | - | - | - | - | - | - | - | - |
| **Celecoxib** | - | - | - | - | 5 | - | - | - | - | - |
| **Donepezil** | 5 | - | - | - | - | - | - | 5 | - | - |
| **Escitalopram** | - | - | 2 | - | - | - | - | - | - | - |
| **Fluoxetine** | 2 | - | 3 | - | - | - | - | 4 | - | - |
| **FEWP** | - | - | - | - | - | 4 | - | - | - | - |
| **Gabapentin** | 5 | - | - | - | - | - | - | - | - | - |
| **Imipramine** | 3 | - | - | - | - | - | - | 5 | - | - |
| **Ketamine** | - | - | - | - | 2 | - | - | - | - | - |
| **Lamotrigine** | 3 | 3 | 3 | 3 | - | - | - | 2 | - | - |
| **Levetiracetam** | - | - | - | - | 5 | - | - | - | - | - |
| **Levothyroxine (L-T4)** | - | - | - | - | 4 | - | - | - | - | - |
| **Lisdexamfetamine** | - | - | - | - | 5 | - | - | - | - | - |
| **Lithium** | 4 | - | - | - | - | - | 2 | - | - | 5 |
| **L-sulpiride** | - | - | - | - | - | - | - | 3 | - | - |
| **Lurasidone** | 2 | 2 | - | 3 | 2 | - | - | - | - | 3 |
| **memantine** | - | - | - | - | - | - | 5 | - | - | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **modafinil** | - | - | - | - | 2 | - | - | - | - | - |
| **OFC** | 2 | 2 | - | 3 | - | - | - | - | - | - |
| **Olanzapine** | 1 | 1 | - | 3 | - | - | - | - | - | - |
| **Oxcarbazepine** | - | - | - | - | - | - | - | 4 | - | - |
| **Paroxetine** | 5 | 5 | 5 | - | 5 | Neg | - | 5 | 5 | 3 |
| **Phenelzin** | 3 | - | - | - | - | - | - | - | - | - |
| **Pioglitazone** | - | - | - | - | - | - | - | 2 | - | - |
| **Pramipexole** | - | - | - | - | 2 | - | - | - | - | - |
| **Pregnenolone** | - | - | - | - | 5 | - | - | - | - | - |
| **Quetiapine** | 1 | 3 | 3 | 3 | - | - | - | - | - | 3 |
| **Risperidone** | - | - | - | - | 5 | - | - | - | - | 5 |
| **TMS** | 5 | - | - | - | - | - | - | - | - | - |
| **tranylcypromine** | 4 | 4 | 4 | - | - | - | - | - | - | - |
| **Valproate** | 3 | 3 | 5 | 3 | - | - | - | - | - | 3 |
| **Venlafaxine** | 4 | 4 | 4 | - | - | - | - | - | - | - |
| **Ziprasidone** | 5 | 5 | - | - | 5 | - | 5 | 5 | 5 | 5 |

**Table 3**: Acute depression treatment phase, grading on basis of efficacy (treatment phase up to 12 weeks). The treatment options are rated according to the rating system shown in table 1
- : no data
Cbz: Carbamazepine
ECT: Electroconvulsive therapy
FEWP: Free and Easy Wanderer Plus
Lam: Lamotrigine
Li: Lithium
MS: Mood Stabilizer

OFC: Olanzapine Fluoxetine Combination
TMS: Transcranial Magnetic Stimulation
Val: Valproate

| agent/modality (alphabetical order) | index episode | Enriched sample | Any episode | Manic | Depressive |
|---|---|---|---|---|---|
| **Aripiprazole** | m* | yes | - | 1 | 5 |
| **Carbamazepine** | - | - | 4 | 4 | 4 |
| **Fluoxetine** | d | Yes | - | - | 2 |
| **Imipramine** | d | ? | 5 | 5 | 5 |
| **Lamotrigine** | m/d | yes | 1 | 3 | 1 |
| **Lithium** | m/d | No | 1 | 1 | 3 |
| **Olanzapine** | m | Yes/No | 1 | 1 | 1 |
| **Paliperidone** | m | yes | 1 | 2 | 5 |
| **Quetiapine** | m/d | yes | 2 | 2 | 2 |
| **Risperidone, LAI** | m | yes | 1 | 1 | 5 |
| **Valproate** | m | yes | 4 | 4 | 3 |

**Table 4**: Monotherapy treatment during the maintenance phase, grading on basis of efficacy. The treatment options are rated according to the rating system shown in table 1

Enriched sample: the sample is enriched on the basis of remission after treatment with the agent under consideration during the acute phase (index episode)

- : no data

m: mania/mixed, d: depression, m/d: both mania and depression

| | | | overall | | | | manic | | | depressive | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **agent/modality (alphabetical order)** | **index episode** | **Enriched sample** | **MS** | **Lam** | **Li** | **Val** | **MS** | **Lam** | **Li** | **MS** | **Lam** | **Li** | **Val** |
| **Aripiprazole** | m* | yes | 2 | 5 | - | 5 | 2 | 5 | - | 5 | 5 | - | - |
| **CBT** | d | No | 2 | - | - | - | - | - | - | - | - | - | - |
| **Gabapentin** | - | - | - | - | - | - | 4 | - | - | - | - | - | - |
| **Imipramine** | d | ? | - | - | 5 | | - | - | - | - | - | - | - |
| **Lamotrigine** | m/d | yes | - | - | 4 | | - | - | - | - | - | - | 5 |
| **Lithium** | m/d | No | - | 4 | - | - | - | - | - | - | - | - | - |
| **Memantine** | - | - | - | - | - | 5 | - | - | - | - | - | - | - |
| **N-acetyl cysteine** | d | Yes | 4 | - | - | - | - | - | - | - | - | - | - |
| **Olanzapine** | m | Yes/No | 4 | - | - | - | - | - | - | - | - | - | - |
| **Oxcarbazepine** | - | - | - | - | 5 | - | - | - | 5 | - | - | 5 | - |
| **Paroxetine** | - | - | 3 | - | - | - | - | - | - | 3 | - | - | - |
| **Perphenazine** | m | yes | 5 | - | - | - | - | - | - | - | - | - | - |
| **Phenytoin** | euth | No | 2 | - | - | - | - | - | - | - | - | - | - |
| **Quetiapine** | m/d | yes | 1 | - | - | - | 1 | - | - | 1 | - | - | - |
| **Risperidone, Long-acting Injectable** | m | yes | 2 | - | - | - | 2 | - | - | - | - | - | - |
| **Valproate** | m | yes | - | - | - | - | - | - | - | - | 5 | - | - |
| **Ziprasidone** | m | yes | 2 | - | - | - | - | - | - | - | - | - | - |

**Table 5**: Combination treatment during the maintenance phase, grading on basis of efficacy. The treatment options are rated according to the rating system shown in table 1.
Enriched sample: the sample is enriched on the basis of remission after treatment with the agent under consideration during the acute phase (index episode)
- : no data m: mania/mixed, d: depression, m/d: both mania and depression

CBT: Cognitive Behavioural Therapy
Cbz: Carbamazepine
Lam: Lamotrigine
Li: Lithium
MS: Mood Stabilizer
Val: Valproate

| | Acute phase | | | | Maintenance phase | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Monotherapy | | Combination with MS | | Monotherapy | Combination | | | | |
| agent/modality (alphabetical order) | manic component | Depressive component | Manic component | Depressive component | | MS | Cbz | Lam | Li | Val |
| **Aripiprazole** | 3 | 3 | - | - | - | 2 | - | 5 | - | - |
| **Asenapine** | 4 | 4 | - | - | - | - | - | - | - | - |
| **Carbamazepine** | 3 | 3 | - | - | - | - | - | - | - | - |
| **Celecoxib** | - | - | 5 | 5 | - | - | - | - | - | - |
| **Haloperidol** | - | - | 5 | 5 | - | - | - | - | - | - |
| **Lithium** | 5 | - | - | - | - | - | - | - | - | - |
| **OFC** | 4 | 4 | - | - | - | - | - | - | - | - |
| **Olanzapine** | 3 | 3 | 2 | 2 | 1 | - | - | - | - | - |
| **Paliperidone** | 3 | 5 | - | - | - | - | - | - | - | - |
| **Quetiapine** | 5 | - | - | - | - | - | - | - | - | - |
| **Risperidone** | 3 | - | 5 | 5 | - | - | - | - | - | - |
| **Valproate** | 3 | 4 | - | - | - | - | - | - | - | - |
| **Ziprasidone** | 4 | 4 | - | - | - | - | - | - | - | - |

**Table 6:** Treatment of mixed episodes. The treatment options are rated on the basis of efficacy according to the rating system shown in table 1
- : no data
Cbz: Carbamazepine Lam: Lamotrigine Li: Lithium MS: Mood Stabilizer OFC: Olanzapine-Fluoxetine Combination
Val: Valproate

| agent/modality (alphabetical order) | acute mania | depression | maintenance |
|---|---|---|---|
| **Aripiprazole** | 3 | - | 3 |
| **Carbamazepine** | - | - | 2 (Li + Cbz) |
| **Lamotrigine** | - | - | 5 |
| **Lithium** | 4 | 3 | 2 (Li, Li + Cbz) |
| **Olanzapine** | 3 | - | - |
| **Paroxetine** | - | 5 | - |
| **Quetiapine** | 3 | 2 | 2 (Quet+ Val/Li) |
| **Risperidone, Long-acting Injectable** | - | - | 2 (RLAI+TAU) |
| **Valproate** | 4 | 4 | - |

**Table 7:** Treatment of rapid cycling patients during the different phases of BD. The treatment options are rated on the basis of efficacy according to the rating system shown in table 1
- : no data
Cbz: Carbamazepine
Li: Lithium
Quet: Quetiapine
RLAI: Risperidone Long-acting Injectable
TAU: Treatment As Usual
Val: Valproate

| Intervention | Efficacy | | | | | |
|---|---|---|---|---|---|---|
| | **Relapse/ recurrence** | **Manic symptoms** | **Depressive symptoms** | **Anxiety** | **Neurocognition** | **Overall functioning** |
| CBT | 5 | - | 3 | - | - | - |
| Psychoeducation | 3 | 5 | 5 | - | - | 3 |
| IPSRT | 4 | - | - | - | - | - |
| Family intervention | 5 | 5 | 5 | - | - | 5 |
| Intensive psychosocial intervention | - | - | - | - | - | - |
| Cognitive remediation | 5 | 5 | 5 | - | 5 | 5 |
| Mindfulness based interventions | 5 | 5 | 5 | 3 | - | - |

**Table 8: G**rading of the evidence for the efficacy of non-biological treatment options. The treatment options are rated according to the rating system shown in table 1

- : no data

CBT: Cognitive Behavioral Treatment

IPSRT: InterPersonal and Social Rhythms Therapy

| agent/modality (alphabetical order) | grade | comments |
|---|---|---|
| Agomelatine | 2 | Liver enzymes induction |
| Allopurinol | 2 | Swelling of mouth and lips, severe skin rashes, infections, eye irritation, hepatitis, appetite and weight loss, and painful or bloody urination |
| Aripiprazole | 1 | |
| Armodafinil/modafinil | 2 | Stimulant, risk for abuse |
| Asenapine | 1 | |
| Bupropion | 1 | |
| Carbamazepine | 2 | Hepatic enzymes induction, many adverse effects |
| Cariprazine | 1 | |
| Celecoxib | 1 | |
| Chlorpromazine | 1 | |
| Clozapine | 3 | Potentially lethal agranulocytosis, metabolic syndrome |
| Donepezil | 1 | |
| ECT | 2 | Not preferred by patients, mild cognitive problems |
| Escitalopram | 1 | |
| Eslicarbazepine | 1 | |
| Fluoxetine | 1 | |
| FEWP | 1 | |
| Gabapentin | 1 | |
| Haloperidol | 2 | EPS, Tardive dyskinesia, neuroleptic malignant syndrome, switch risk |
| Imipramine | 2 | Cardiac side effects, many adverse effects, switch risk |
| Ketamine | 3 | Stimulant |
| L-sulpiride | 1 | |
| Lamotrigine | 2 | Good overall tolerability but potentially lethal skin reaction which can be avoided by slow titration |
| Levetiracetam | 3 | Induction of suicidality |
| levothyroxine (L-T4) | 2 | Mild cardiovascular, skin and bone adverse effects |
| Licarbazepine | 1 | |
| Lisdexamfetamine | 3 | High risk for abuse and dependence |
| Lithium | 2 | Many adverse effects, weight gain, toxicity |
| Loxapine inhalant | 1 | |
| Lurasidone | 1 | |
| N-acetyl cysteine | 1 | |
| Memantine | 1 | |
| Medroxyprogesterone | 1 | |
| Modafinil | 2 | Stimulant, risk for abuse |
| Olanzapine | 2 | Metabolic syndrome |
| Oxcarbazepine | 1 | |

| | | |
|---|---|---|
| Paliperidone | 1 | |
| Paroxetine | 1 | |
| Perphenazine | 2 | Switch risk, EPS, tardive dyskinesia, neuroleptic malignant syndrome |
| Phenytoin | 2 | Many adverse effects |
| Phenelzin | 2 | Many adverse effects |
| Pimozide | 2 | EPS, tardive dyskinesia, neuroleptic malignant syndrome |
| Pioglitazone | 2 | Not recommended in patients with diabetes mellitus type I and in liver disease. Absolute contraindication in heart failure patients |
| Pramipexole | 2 | Adverse effects include the induction of problematic behaviours and psychotic symptoms |
| Pregnenolone | 2 | Not well studied |
| Quetiapine | 1 | |
| Risperidone | 1 | |
| RLAI | 1 | |
| Sertraline | 1 | |
| Tamoxifen | 3 | Deep vein thrombosis, cognitive disorder |
| TMS | 1 | |
| Topiramate | 3 | Induction of depression and suicidality |
| Tranylcypromine | 2 | Many adverse effects |
| Valproate | 1 | Cautious use in women of childbearing age |
| Venlafaxine | 2 | Switch risk |
| Verapamil | 1 | |
| Ziprasidone | 2 | QTc prolongation, patients should undergo cardiologic examination before receiving ziprasidone |

**Table 9:** Grading of treatment options according to safety issues, according to the system shown in table 1.
ECT: Electroconvulsive Therapy
EPS: Extrapyramidal Signs
FEWP: Free and Easy Wanderer Plus
RLAI: Risperidone Long-acting Injectable
TMS: Transcranial Magnetic Stimulation

| | Treatment phase | | |
|---|---|---|---|
| **agent/modality (alphabetical order)** | **Acute mania** | **depression** | **maintenance** |
| **Aripiprazole** | 5 | 5 | 5 |
| **Asenapine** | 5 | - | 5 |
| **Bupropion** | - | 5 | - |
| **Carbamazepine** | 5 | - | 5 |
| **ECT** | - | 4 | - |
| **Escitalopram** | - | 5 | - |
| **Fluoxetine** | - | - | 5 |
| **Haloperidol** | 4 | - | 4 |
| **Imipramine** | - | 3 | 2 |
| **Lamotrigine** | 5 | - | 5 |
| **Lithium** | 5 | - | 5 |
| **OFC** | - | 5 | 5 |
| **Olanzapine** | 5 | 5 | 5 |
| **Paliperidone** | 5 | - | 5 |
| **Paroxetine** | - | 5 | 5 |
| **Perphenazine** | 4 | - | 2 |
| **Quetiapine** | 5 | 5 | 5 |
| **RLAI** | 5 | - | 5 |
| **Sertraline** | - | - | 5 |
| **Valproate** | 5 | - | 5 |
| **Venlafaxine** | - | 3 | - |
| **Ziprasidone** | 5 | - | 5 |

**Table 10:** Risk of various agents to induce the opposite mood pole (switch risk). The treatment options are rated in an analogous way to the rating system shown in table 1 as 'efficacy to induce the opposite pole'
- : no data
ECT: Electroconvulsive Therapy
OFC: Olanzapine-fluoxetine combination
RLAI: Risperidone Long-acting Injectable

| agent/modality | Recommendation level | Recommended dosage (mg/day) |
|---|---|---|
| Aripiprazole | 1 | 15-30 mg/day |
| Asenapine | 1 | 10-20 mg/day |
| Cariprazine | 1 | 3-12 mg/day |
| Paliperidone | 1 | 3-12 mg/day |
| Quetiapine | 1 | 400-800 mg/day |
| Risperidone | 1 | 2-6 mg/day |
| Valproate | 1 | 1200-3000 mg/day (loading dose 20-30 mg/kg body weight; serum level 75-150 mg) |
| Carbamazepine | 2 | 600-1200 mg/day (serum level 4-15 mg/l) |
| Haloperidol | 2 | 5-20 mg/day |
| Lithium | 2 | 600-1200 mg/day (serum level 0.8-1.3 mmol) |
| Olanzapine | 2 | 10-20 mg/day |
| ECT | 3 | |
| Oxcarbazepine | 4 | 900-1800 mg/day |
| Chlorpromazine | 4 | 300-1000 mg/day |
| Pimozide | 4 | 2-16 mg/day |
| Tamoxifen | 4 | 40-80 mg/day |
| Ziprasidone | 4 | 80-160 mg/day` |
| Eslicarbazepine | 5 | |
| Gabapentin | 5 | |
| Lamotrigine | 5 | |
| Licarbazepine | 5 | |
| TMS | 5 | |
| Topiramate | 5 | |
| Verapamil | 5 | |

**Table 11:** Levels of recommendation concerning monotherapy in acute mania and recommended dosages for medication options
NR: not recommended
ECT: Electroconvulsive therapy
TMS: Transcranial Magnetic Stimulation

| agent/modality | MS | Li | Val | Cbz | FGAs |
|---|---|---|---|---|---|
| Asenapine | 1 | - | - | - | - |
| Haloperidol | 2 | 2 | 2 | 2 | - |
| Olanzapine | 2 | - | 2 | 5 | - |
| Aripiprazole | 2 | - | - | - | - |
| Medroxyprogesterone | 5 | - | - | - | - |
| Celecoxib | - | - | 2 | - | - |
| Quetiapine | 3 | 3 | - | - | - |
| Risperidone | 3 | - | 5 | - | - |
| Tamoxifen | 4 | 4 | - | - | - |
| Allopurinol | 5 | 2 | - | - | 5 |
| Paliperidone | 5 | - | - | - | - |
| Ziprasidone | 5 | - | - | - | - |
| Gabapentin | 5 | - | - | - | - |
| Topiramate | 5 | - | - | - | - |
| Lamotrigine | - | - | - | - | - |
| Lithium | - | - | - | 2 | - |
| Oxcarbazepine | - | 4 | - | - | - |
| Valproate | - | - | - | - | 2 |

**Table 12:** Recommendation levels for combination treatment for acute mania
MS: mood stabilizer
Li: lithium, Val: valproate, Cbz: carbamazepine, FGAs: first generation antipsychotics

| agent/modality | Recommendation level |
|---|---|
| Quetiapine | 3 |
| Aripiprazole | 3 |
| Olanzapine | 3 |
| Valproate | 4 |
| Lithium | 4 |

**Table 13:** Recommendation levels for monotherapy in rapid cycling patients in an acute manic episode

| agent/modality | Therapeutic effect on | | |
|---|---|---|---|
| | Overall on manic episode | Concomitant Depressive symptoms | Psychotic symptoms |
| **Quetiapine** | 1 | 3 | 3 |
| **Risperidone** | 1 | 3 | 3 |
| **Aripiprazole** | 1 | 5 | 3 |
| **Asenapine** | 1 | 5 | - |
| **Olanzapine** | 2 | 3 | 3 |
| **Carbamazepine** | 2 | 5 | - |
| **Cariprazine** | 1 | 5 | - |
| **Haloperidol** | 2 | 5 | 3 |
| **Lithium** | 2 | 5 | 3 |
| **Tamoxifen** | 4 | 5 | 4 |
| **Valproate** | 1 | 5 | - |
| **Ziprasidone** | 2 | 5 | 3 |

**Table 14:** Recommendation levels for monotherapy in patients in an acute manic episode and the specific effect on concomitant depressive symptoms (mixed features) and psychotic features.

| | monotherapy | | combination with MS | |
|---|---|---|---|---|
| **agent/modality** | **manic component** | **Depressive component** | **manic component** | **Depressive component** |
| **Olanzapine** | 3 | 3 | 2 | 2 |
| **Asenapine** | 3 | 3 | - | - |
| **Aripiprazole** | 3 | 3 | - | - |
| **Carbamazepine** | 3 | 3 | - | - |
| **Valproate** | 3 | 4 | - | - |
| **Paliperidone** | 3 | 5 | - | - |
| **Risperidone** | 3 | - | 5 | 5 |
| **OFC** | 4 | 4 | - | - |
| **Ziprasidone** | 4 | 4 | - | - |
| **Lithium** | 5 | - | - | - |
| **Quetiapine** | 5 | - | - | - |
| **Celecoxib** | - | - | 5 | 5 |
| **Haloperidol** | - | - | 5 | 5 |

**Table 15:** Recommendation levels for monotherapy and combination treatment in patients in a DSM-IV-TR mixed episode and the specific effect on the manic and the depressive component.
MS: mood stabilizer
OFC: olanzapine-fluoxetine combination

| Step | First | Second | Third | Fourth | Fifth |
|---|---|---|---|---|---|
| **All cases** | Discontinue treatment with antidepressants | | | | |
| **Rapid cycling** | Start with aripiprazole or quetiapine monotherapy.<br>In non-psychotic cases valproate is also an option<br>Take into consideration the previous history of psychotic features. | Olanzapine or lithium monotherapy | Combination treatment of lithium or valproate with quetiapine, or risperidone. | Apply ECT on top of pharmacological treatment.<br><br>Monotherapy with chlorpromazine, pimozide, or tamoxifen.<br>Options are also combination treatments of lithium or valproate plus tamoxifen or the combination of risperidone or oxcarbazepine plus lithium | Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist, ECT if not applied earlier |
| **Non-Rapid cycling with psychotic features** | Start with aripiprazole, cariprazine, paliperidone, quetiapine or risperidone monotherapy. | Monotherapy with haloperidol, lithium, olanzapine or ziprasidone or combination treatment of lithium or valproate with aripiprazole, haloperidol or olanzapine. Lithium combinations with allopurinol* is also an option. Another combination is valproate plus an FGA. | | | |
| **Non rapid cycling without Psychotic features** | All options which are suitable in the presence of psychotic features and also valproate and asenapine monotherapy are a choice.<br>*Take into consideration the previous history of psychotic features.* | All options which are suitable in the presence of psychotic features and also monotherapy with carbamazepine or valproate plus celecoxib* are an option<br>*Take into consideration the previous history of psychotic features.* | | | |
| **Mixed Features** | Start with quetiapine or risperidone monotherapy. | Olanzapine monotherapy | | | |

| | | | | | |
|---|---|---|---|---|---|
| **All other cases** | If the patient is already under one of the above 'first step' monotherapy or under combination therapy of any kind and response is unsatisfactory, switch into another 'first step' monotherapy.<br>In case the personal history of the patient suggests this is not an option, proceed to next step and switch to the closest second step treatment option. | Proceed to next step | | | |
| **Mixed episode** | Start with combination of olanzapine plus valproate or maybe lithium | Monotherapy with olanzapine, aripiprazole or carbamazepine. | Valproate monotherapy | OFC or ziprasidone monotherapy. | |

**Table 16:** Precise evidence-based alrogithm to treat acute manic episodes on the basis of specific clinical characteristics
* no wide clinical experience

CBT: Cognitive Behavioral Treatment
Cbz: Carbamazepine
ECT: Electroconvulsive therapy
IPSRT: InterPersonal and Social Rhythms Therapy
Lam: Lamotrigine
Li: Lithium
MS: Mood Stabilizer
OFC: Olanzapine Fluoxetine Combination
rTMS: repetitive Transcranial Magnetic Stimulation
Val: Valproate

| | CINP 2016 | WFSBP 2013* | CANMAT & ISBD 2013 | NICE 2014** | BAP 2016** |
|---|---|---|---|---|---|
| Aripiprazole | 1 | 1 | 1 | - | 3 |
| Asenapine | 1 | 3 | 1 | - | 3 |
| Cariprazine | 1 | - | 3 | - | 3 |
| Paliperidone | 1 | 3 | 1 | - | 3 |
| Quetiapine | 1 | 3 | 1 | 1 | 1 |
| Risperidone | 1 | 1 | 1 | 1 | 1 |
| Valproate | 1 | 1 | 1 | 1 | 2 |
| Carbamazepine | 2 | 3 | 2 | - | 3 |
| Haloperidol | 2 | 3 | 2 | 1 | 1 |
| Lithium | 2 | 3 | 1 | 1 | 3 |
| Olanzapine | 2 | 3 | 1 | 1 | 1 |
| Ziprasidone | 2 | 1 | 1 | - | 3 |
| ECT | 3 | 4 | 2 | - | 3 |
| Oxcarbazepine | 4 | 4 | 3 | - | - |
| Chlorpromazine | 4 | 3 | 3 | - | 3 |
| Pimozide | 4 | 3 | - | - | 3 |
| Tamoxifen | 4 | 3 | 3 | - | - |
| Eslicarbazepine | NR | - | - | - | - |
| Gabapentin | NR | NR | NR | NR | - |
| Lamotrigine | NR | NR | NR | NR | - |
| Licarbazepine | NR | - | - | - | - |
| rTMS | NR | - | - | - | - |
| Topiramate | NR | NR | NR | NR | - |
| Verapamil | NR | - | - | - | - |
| Phenytoin | - | 3 | - | - | - |
| Clozapine | - | 4 | 3 | - | 3 |
| Amisulpride | - | 4 | - | - | 3 |
| Clonazepam | - | 4 | - | - | - |
| Leviracetam | - | 4 | - | - | - |
| Lorazepam | - | 4 | - | - | - |

**Table 17:** Comparison of the detailed algorithm to previously developed guidelines for acute mania (the grading is not uniform; instead it reflects the grading utilized by individual guidelines and the table aims only to give an image of how different guidelines prioritize treatment options)
Numbers correspond to steps not to efficacy ranking
* NICE and BAP ordering is on the basis of line of treatment
** Step 2 in the WFSBP guideline would be a combination of two grade "1" recommended medication, or switch from one grade "1" medication to another.
ECT: Electroconvulsive treatment
rTMS: repetitive Transcranial Magnetic Stimulation
NR: Not Recommended

| agent/modality | overall | BD-I | BD-II | Depressive core | Comorbid anxiety | Rapid cycling | Recommended Dosage (mg/day) |
|---|---|---|---|---|---|---|---|
| **Quetiapine** | 1 | 3 | 3 | 3 | 3 | 2 | 300-600 mg/day |
| **Lurasidone** | 1 | - | - | 3 | 3 | - | 20-120 mg/day |
| **OFC** | 2 | 2 | - | 3 | - | - | 6+25; 6+50; 12+50 mg/day |
| **Escitalopram** | - | - | 1 | - | - | - | 10 mg/day |
| **Fluoxetine** | 2 | - | 3 | - | - | - | 20-80 mg/day |
| **Olanzapine** | 2 | 4 | - | 3 | - | - | 5-20 mg/day |
| **Carbamazepine** | 3 | - | - | - | - | - | 300-800 mg/day |
| **Valproate** | 3 | 3 | 5 | 3 | 3 | 4 | 500-2500 mg/day (50-100 mcg/ml) |
| **Aripiprazole** | 3 | 3 | - | - | - | - | 5-30 mg/day |
| **Imipramine** | 3 | - | - | - | - | - | 75-300 mg/day |
| **Lamotrigine** | 3 | 3 | 3 | 3 | - | - | 50-200 mg/day |
| **Phenelzine** | 3 | - | - | - | - | - | 15-90 mg/day |
| **Lithium** | 4 | - | 4 | - | 5 | 3 | 600-1800 mg/day |
| **Tranylcypromine** | 4 | 4 | 4 | - | - | - | 20-30 mg/day |
| **Venlafaxine** | 4 | 4 | 4 | - | - | - | 75-225 mg/day |
| **Paroxetine** | 5 | 5 | 5 | - | 3 | 5 | 20 mg/day |
| **Ziprasidone** | 5 | 5 | - | - | 5 | - | |
| **Gabapentin** | 5 | - | - | - | - | - | |
| **rTMS** | 5 | - | - | - | - | - | |
| **Risperidone** | - | - | - | - | 5 | - | |

**Table 18:** Level of recommendation concerning monotherapy in acute bipolar depression, in comorbid conditions and rapid cycling patients and recommended dosages for medication options
OFC: olanzapine-fluoxetine combination, rTMS: repetitive Transcranial Magnetic Stimulation
NR: not recommended

| agent/modality | MS | Cbz | Lam | Li | Val |
|---|---|---|---|---|---|
| Lurasidone | 2 | - | - | - | - |
| Modafinil | 2 | - | - | - | - |
| Pramipexole | 2 | - | - | - | - |
| Pioglitazone | - | - | - | 2 | - |
| Armodafinil | 4 | - | - | - | - |
| Ketamine | 4 | - | - | - | - |
| Paroxetine | 5 | 5 | - | 5 | 5 |
| Ziprasidone | 5 | - | 5 | 5 | 5 |
| Bupropion | 5 | - | - | - | - |
| Celecoxib | 5 | - | - | - | - |
| Levetiracetam | 5 | - | - | - | - |
| Levothyroxine (L-T4) | 4 | - | - | - | - |
| Risperidone | 5 | - | - | - | - |
| Lithium | - | - | 2 | - | - |
| Memantine | - | - | 5 | - | - |
| FEWP | - | 4 | - | - | - |
| Oxcarbazepine | - | - | - | 4 | - |
| Lamotrigine | - | - | - | 2 | - |
| L-sulpiride | - | - | - | 3 | - |
| Fluoxetine | - | - | - | 4 | - |
| Agomelatine | 5 | - | - | 5 | 5 |
| Aripiprazole | - | - | - | 5 | - |
| Imipramine | - | - | - | 5 | - |

**Table 19:** Level of recommendation concerning combination treatment in acute bipolar depression
MS: mood stabilizer
Cbz: carbamazepine
Lam: lamotrigine
Val: valproate
FEWP: Free and Easy Wanderer Plus (herbal agent)

| Steps | First | Second | Third | Fourth | Fifth |
|---|---|---|---|---|---|
| **Overall** | Start with quetiapine or lurasidone<br>Consider CBT as add-on to medication and according to the patient preference and to availability. Never consider CBT as monotherapy | Add a mood stabilizer on lurasidone, modafinil or pramipexole<br>Lithium plus lamotrigine, or pioglitazone*<br>Olanzapine monotherapy or OFC | Valproate, aripiprazole, imipramine, phenelzin, carbamazepine or lamotrigine monotherapy<br>Lithium plus L-sulpiride | Tranylcypromine or lithium monotherapy<br>Venlafaxine preferably in combination with an antimanic agent<br>Armodafinil or ketamine on a moodstabilizer<br>Lithium plus fluoxetine<br>Carbamazepine plus FEWP<br>Mood stabilizer plus levothyroxine (L-T4)<br>Lithium plus oxcarbazepine | ECT or various combinations of medication according to anecdotal knowledge or the personal experience of the therapist |
| **Rapid cycling** | | If BD-I start with valproate, in BD-II with lithium | | | |
| **No rapid cycling** | | If BD-II start with escitalopram or fluoxetine monotherapy | | | |
| **Comorbid anxiety** | | Add paroxetine, quetiapine, valproate or lurasidone and consider Mindfulness based interventions as add-on to these agents | | | |

**Table 20:** Precise algorithm to treat acute bipolar depressive episodes on the basis of specific clinical characteristics
* no wide clinical experience

CBT: Cognitive Behavioral Treatment
Cbz: Carbamazepine
ECT: Electroconvulsive therapy
FEWP: Free and Easy Wanderer Plus (herbal agent)

IPSRT: InterPersonal and Social Rhythms Therapy
Lam: Lamotrigine
Li: Lithium
MS: Mood Stabilizer
OFC: Olanzapine Fluoxetine Combination
rTMS: repetitive Transcranial Magnetic Stimulation
Val: Valproate

| | CINP 2016 | WFSBP 2013* | CANMAT & ISBD 2013 | NICE 2014** | BAP 2016** |
|---|---|---|---|---|---|
| Lurasidone | 1 | - | 2 | - | 1 |
| Quetiapine | 1 | 1 | 1 | 1 | 1 |
| Escitalopram | 2*** | - | - | - | 3 |
| Fluoxetine | 2*** | 1 | - | - | 3 |
| Olanzapine | 2 | 1 | 3 | 1 | 1 |
| OFC | 2 | 1 | 1 | 1 | 1 |
| Aripiprazole | 3 | NR | NR | - | - |
| Imipramine | 3 | | | | 4 |
| Lamotrigine | 3 | 1 | 1 | 1 | 2 |
| Phenelzin | 3 | | | | - |
| Valproate | 3 | 1 | 2 | 1 | - |
| Carbamazepine | 3 | 1 | 3 | - | - |
| Lithium | 4 | 1 | 1 | 1 | 3 |
| Tranylcypromine | 4 | - | - | - | 4 |
| ECT | 5 | - | 3 | - | 5 |
| Gabapentin | NR | - | NR | - | - |
| Leviracetam | - | - | NR | - | - |
| L-thyroxine | - | - | - | - | - |
| Paroxetine | NR | NR | - | - | 3 |
| Risperidone | - | - | NR | - | - |
| rTMS | NR | - | - | - | - |
| Ziprasidone | NR | NR | NR | - | - |

**Table 21:** Comparison of the presise algorithm to previously developed guidelines for acute bipolar depression concerning monotherapy (the grading is not uniform; instead it reflects the grading utilized by individual guidelines and the table aims only to give an image of how different guidelines prioritize treatment options)
Numbers correspond to steps not to efficacy ranking
*WFSBP: Recommendation only reflects monotherapy not considering evidence derived from combination treatment (except OFC)
** NICE and BAP ordering is on the basis of line of treatment
*** against BD-II depression
NICE ordering is on the basis of line of treatment
ECT: Electroconvulsive treatment
OFC: Olanzapine-Fluoxetine Combination
rTMS: repetitive Transcranial Magnetic Stimulation
NR: Not Recommended

| agent/modality | index episode | Enriched sample | Manic | depressive | Mixed | Rapid cycling | Recommended dosage |
|---|---|---|---|---|---|---|---|
| **Quetiapine** | m/d | yes | 2 | 2 | - | Quet+ Val/Li (3) | 300-800 mg/day |
| **Olanzapine** | m | Yes/No | 2 | 2 | 2 | - | 5-20 mg/day |
| | | | | | | | |
| **Lithium** | m/d | No | 2 | 3 | - | Li, Li + Cbz (3) | 0.6-1.2 mEq/l |
| **Lamotrigine** | m/d | yes | 3 | 2 | - | 5 | 50-400 mg/day |
| | | | | | | | |
| **Aripiprazole** | m | yes | 1 | 5 | - | 3 | 10-30 mg/day |
| **RLAI** | m | yes | 1 | 5 | - | RLAI+TAU (3) | 25-50 mg/biweekly |
| **Paliperidone** | m | yes | 2 | 5 | - | - | 3-12 mg/day |
| **Valproate** | m | yes | 4 | 3 | - | - | 45-100 mg/l |
| **Ziprasidone** | m | yes | - | - | - | - | 80-160 mg/day |
| **Perphenazine** | m | yes | - | - | - | - | |
| | | | | | | | |
| **Imipramine** | d | ? | 5 | 5 | - | - | |
| **Fluoxetine** | d | Yes | - | 2 | - | - | 10-40 mg/day |
| **CBT** | d | No | - | - | - | - | |
| **N-acetyl cysteine** | d | Yes | - | - | - | - | |
| **Carbamazepine** | - | - | 4 | 4 | - | Li + Cbz (3) | 4-12 mg/l |

**Table 22:** Level of recommendation concerning monotherapy during the maintenance phase and in relationship to index episode, composition of the sample, presence of rapid cycling and the efficacy in the prevention of mainic, mixed or depressive episodes as well as recommended dosages

Enriched sample: the sample is enriched on the basis of remission after treatment with the agent under consideration during the acute phase (index episode)

CBT: Cognitive Behavioural Therapy, Cbz: carbamazepine, Li: lithium, Quet: quetiapine, RLAI: Risperidone Long Acting Injection, TAU: Treatment As Usual, Val: valproate

| agent/modality | MS | Cbz | Lam | Li | Val |
|---|---|---|---|---|---|
| Quetiapine | 1 | - | - | - | - |
| Aripiprazole | 2 | - | 5 | - | 5 |
| RLAI | 2 | - | - | - | - |
| CBT | 2 | - | - | - | - |
| Phenytoin | 2 | - | - | - | - |
| Paroxetine | 3 | - | - | - | - |
| Psychoeducation | 3 | - | - | - | - |
| Olanzapine | 4 | - | - | - | - |
| Ziprasidone | 4 | - | - | - | - |
| N-acetyl cysteine | 4 | - | - | - | - |
| Imipramine | - | - | - | 5 | - |
| Memantine | 5 | - | - | - | - |
| Oxcarbazepine | - | - | - | 5 | - |
| Lithium | - | - | 4 | - | - |
| Perphenazine | 5 | - | - | - | - |

**Table 23:** Level of recommendation concerning combination treatment during the maintenance phase
CBT: Cognitive Behavioral Therapy, Cbz: carbamazepine, Lam: lamotrigine
Li: lithium, MS: mood stabilizer, RLAI: Risperidone Long Acting Injection,
Val: valproate

<table>
<tr><th>Step</th><th>First</th><th>Second</th><th>Third</th><th>Fourth</th><th>Fifth</th></tr>
<tr><td>Depressive predominant polarity or<br><br>No predominant polarity</td><td>Quetiapine or olanzapine monotherapy</td><td>Add fluoxetine or lamotrigine</td><td>Add N-acetylcysteine</td><td>If depressive episodes keep emerging add an agent with proven efficacy against acute bipolar depression no matter whether it has proven maintenance efficacy. Consider adding venlafaxine or lithium plus lamotrigine.</td><td rowspan="4">Consider any combinations from steps 1-4 which have not been tried<br>Consider maintenance ECT<br>Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist<br><br>Consider IPSRT as add-on to medication on the basis of clinical judgement of the therapist and according to the patient preference and to availability. Never consider IPSRT as monotherapy</td></tr>
<tr><td>Manic predominant polarity</td><td>Start with lithium, aripiprazole, olanzapine, paliperidone, quetiapine or risperidone (including RLAI) monotherapy</td><td rowspan="3">Add lithium on the first step option<br><br>Lithium plus carbamazepine<br><br>Quetiapine plus lithium or valproate</td><td>If manic episodes keep emerging add RLAI on current treatment if not already in place<br>Add N-acetylcysteine</td><td>If manic episodes keep emerging add an agent which has proven efficacy against acute mania no matter whether it has proven maintenance efficacy. Consider haloperidol or lithium plus lamotrigine</td></tr>
<tr><td>Mixed episodes are frequent</td><td>Olanzapine or aripiprazole plus a mood stabilizer</td><td rowspan="2">Add valproate, carbamazepine or lamotrigine on second step treatment</td><td rowspan="2">Proceed to next step</td></tr>
<tr><td>Rapid cycling</td><td>Lithium monotherapy</td></tr>
<tr><td>All cases</td><td colspan="5">Consider CBT or psychoeducation as add-on to medication on the basis of clinical judgement of the therapist and according to the patient preference and to availability. Never consider CBT or psychoeducation as monotherapy</td></tr>
</table>

**Table 24:** Precise algorithm to treatment during the maintenance phase for bipolar disorder on the basis of specific clinical characteristics

CBT: Cognitive Behavioral Treatment
Cbz: Carbamazepine
ECT: Electroconvulsive therapy
IPSRT: InterPersonal and Social Rhythms Therapy

Lam: Lamotrigine
Li: Lithium
MS: Mood Stabilizer

| | CINP 2016 | WFSBP 2013* | CANMAT & ISBD 2013 | NICE 2014** | BAP 2016** |
|---|---|---|---|---|---|
| Aripiprazole | 1 | 1 | 1 | - | 3 |
| Lithium | 1 | 1 | 1 | 1 | 1 |
| Olanzapine | 1 | 2 | 1 | 1 | 2 |
| Paliperidone | 1 | 3 | 2 | - | 3 |
| Quetiapine | 1 | 1 | 1 | 1 | 2 |
| Risperidone | 1 | 2 | - | - | 3 |
| RLAI | 1 | - | 1 | - | 2 |
| OFC | 2 | - | 2 | - | - |
| Lamotrigine | 2 | 1 | 1 | - | 2 |
| Carbamazepine | 3 | 4 | 2 | - | 2 |
| Valproate | 3 | 3 | 1 | 1 | 2 |
| Haloperidol | 4 | - | - | - | 3 |
| Venlafaxine | 4 | - | - | - | - |
| ECT | 5 | 4 | 3 | - | - |
| Ziprasidone | 5 | 3 | - | - | 3 |
| Continue most recent episode treatment | NR | - | - | 1 | - |
| Antidepressants | - | 3 | NR | - | 4 |
| Asenapine | - | 4 | 3 | - | 3 |
| Gabapentine | - | 4 | NR | NR | - |
| Topiramate | - | 4 | NR | - | - |

**Table 25:** Comparison of the presise algorithm to previously developed guidelines for maintenance phase concerning monotherapy (the grading is not uniform; instead it reflects the grading utilized by individual guidelines and the table aims only to give an image of how different guidelines prioritize treatment options)
Numbers correspond to steps not to efficacy ranking
*WFSBP: Recommendation grades and subsequent positioning could be either based on efficacy in the prevention of mania, depression or any episode. Thus, numbers do not reflect the sequence of treatment in an individual patient.
** NICE and BAP ordering is on the basis of line of treatment
RLAI: Risperidone Long-Acting Injectable
OFC: Olanzapine-Fluoxetine Combination
ECT: Electro-Convulsive Treatment
NR: not recommended

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**Figure 1**

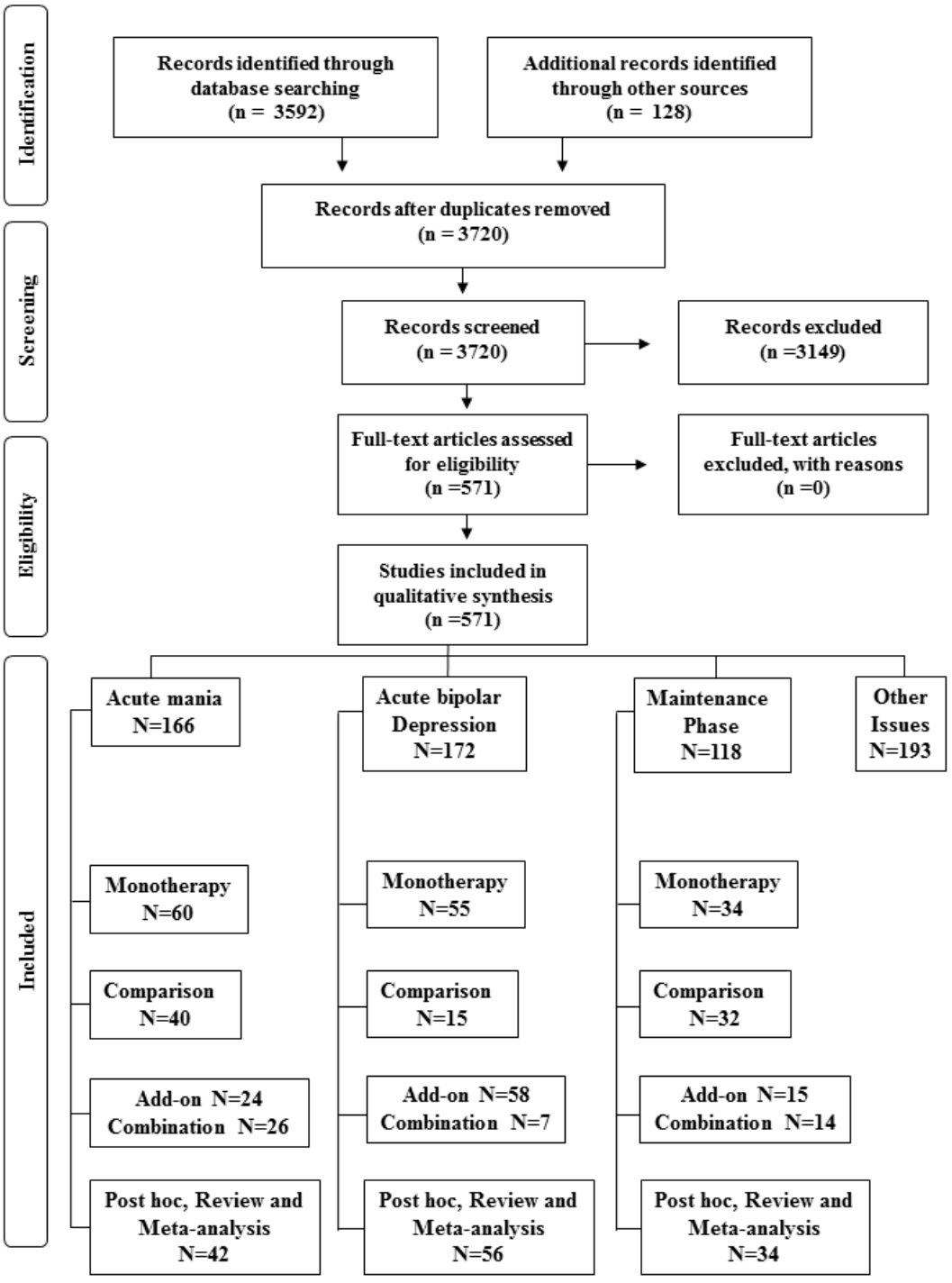

**Figure 2**